EDITORIAL
Wolfgang Grisold

GRANT BESTOWAL
First Recipient of the New EANO Award: Kathy Oliver

REVIEW ARTICLES
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Advances in Technology in Radiation Oncology
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Guido Cavaletti on behalf of the CI-PERINOMS Study Group

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**Hotspots in Neuro-Oncology**

Michael Weller
Editorial

Dear EANO members and readers of the magazine,

This is the second edition of the EANO Neuro-Oncology Magazine and we are glad to say that the statistics of the first issue are promising. The overall hits in the first 3 months amounted to 2045, the main articles were downloaded about 200 times each as PDFs, and the absolute leading article was the paper by Kathy Oliver on patient advocacy. This teaches us a lesson as the awareness of patients and carers is large, and the EANO Magazine may have a potential role in the issues of patients and carers.

Issue 1/2011 contained several important articles such as the EANO guidelines for the diagnosis of glial tumours, technical advances in glioma therapy, tolerability of chemotherapy in the elderly, and the issue of central nervous neurotoxicity in cancer treatment, which is important in oncology. Issue 1/2012 follows along this path and provides articles on molecular markers as well as 2 articles on peripheral neurotoxicity, which is important in the treatment of cancer patients.

These are topics occurring in daily practice, written by experts and of high practical value, and this is the intention of the EANO Neuro-Oncology Magazine – to provide educational resources in the field of neuro-oncology.

In September 2012, the next EANO congress will take place in Marseille. The programme and scientific committees have developed an attractive programme, which will feature developments in diagnosis and treatment. The popular educational day will have an attractive programme and also contributions of scientific and translational background. There will be enough space for free topics and posters and I cordially invite you to participate actively in the scientific programme. It is important for the neuro-oncological community, as well for the authors of scientific papers, to present and discuss results, findings, and observations. As announced previously, we will also have several travel grants for young neuro-oncologists to facilitate attendance since it is one of the missions of the EANO to promote the attendance of young researchers and clinicians.

At the last EANO meeting in Maastricht we arranged an interesting session on neuro-oncology in former Eastern Europe and in North Africa, and it was interesting to learn from the participants how neuro-oncology is practiced. It seems that much work is done, but the interdisciplinary approach towards neuro-oncologic patients will still need some time to grow. At the World Congress of Neurology in Marrakech (http://www.wfneurology.org/), there was much interest in neuro-oncology resulting in a main topic and a teaching course. A few weeks later, the Tunisian Society of Neurology dedicated their yearly meeting to neuro-oncology, which is a great initiative. As previously in Maastricht a meeting will take place in Marseille for national societies of neuro-oncology and we will encourage countries to develop interdisciplinary national societies.

The position of neuro-oncology in Europe also varies from country to country. The intention is to establish a multidisciplinary joint committee for neuro-oncology within the UEMS (http://www.uems.net), which would allow equal access from all participating fields, such as neurosurgery, neurology, radiotherapy, general oncology, pathology, and probably also rehabilitation. The negotiations at the UEMS level are supported by the European Board of Neurology (http://www.uems-neuroboard.org/ebn), which has officially applied for such a status.

Within oncology, and presumably neuro-oncology, the concept of rehabilitation (“cancer rehabilitation”) is developing and will be an important addition to medical and surgical treatment. In particular in neuro-oncological patients, rehabilitation not only of sensory and motor functions, but of cognitive problems is becoming increasingly important and will add to the improved and holistic care of patients.

Last but not least we have to continue our efforts in palliative and supportive care in patients with neuro-oncological diseases, and efforts are made to include glioma into the upcoming guidelines for palliative care of the European Federation of Neurological Societies (http://www.efns.org). The EFNS initiative on e-learning (ebrain) contains a chapter on end-of-life aspects in glioma patients and can be useful for teaching purposes.

Wishing you a successful 2012 and looking forward to meet you in Marseille,

Wolfgang Grisold, MD
President of the EANO
First Recipient of the New EANO Award: Kathy Oliver

On September 25, 2011, Kathy Oliver was awarded the first EANO Award for her efforts as the co-director of the International Brain Tumour Alliance (IBTA, www.theibta.org), an organisation dedicated to the support of brain tumour patients. The award was presented by the president of the EANO, Wolfgang Grisold. The EANO Magazine presents excerpts from her speech.

Thank you so much for the very great honour of this award.

In accepting this very generous award, I must pay tribute to the people who inspire us all to keep researching, to keep treating, to keep advocating, and to keep raising awareness of the terrible challenges of brain tumours. Those people are the brain tumour patients themselves.

Until the harsh realities of a brain tumour diagnosis directly touch your life, it is impossible to imagine what this journey will be like or where it will take you.

My son, Colin, was diagnosed at age 24 with a low-grade glioma and, as many of you know, he died 4 weeks ago from his brain tumour which had by then progressed to a glioblastoma multiforme. He passed away shortly after his 32nd birthday.

Colin continued to work full-time, live independently, and ride his beloved mountain bike up until 5 weeks before he died at home in the arms of his family. He refused to let his brain tumour define his life.

But his journey and that of so many other brain tumour patients whom I’ve met from around the world have certainly defined the work I’ve done on behalf of the International Brain Tumour Alliance over the last half dozen years.

And there is so much work to be done for brain tumour patients: in research labs, in the clinic, in the political and regulatory arenas, and in the wider general public.

I frequently say to people that every morning we should all be asking ourselves: “What can we do for brain tumour patients today?” And every evening we should ask: “Have we done enough?”

I know that certainly not all families have access to this level of support but I believe that we must do all that we can to provide palliative and end-of-life care to brain tumour patients and their families that is as comprehensive, as sensitive, and as widely available as possible.

Colin kept a journal during his brain tumour journey and I would like to share one of the entries from it with you. I hope you derive as much inspiration from his words as I have, and that hearing them will further inspire your crucial and continuing work for brain tumour patients. The entry is from June 6, 2004, the day before Colin’s awake craniotomy and after signing his informed consent for the operation.

“I myself have signed papers today mentioning the word “death” numerous times ... The great unknown, or death, does not scare me. In fact, I welcome the challenge of fighting against it. To be able to stand tall and confront it is the most exciting thing that one can do ... This [challenge] is the real thing ... Bring it on. I am ready to fight and win ...”

On September 25, 2011, Kathy Oliver was awarded the first EANO Award for her efforts as the co-director of the International Brain Tumour Alliance (IBTA, www.theibta.org), an organisation dedicated to the support of brain tumour patients. The award was presented by the president of the EANO, Wolfgang Grisold. The EANO Magazine presents excerpts from her speech.
Management of Gliomas: Relevance of Molecular Markers for Clinical Practice

Michael Weller

Abstract: The histological subtyping and the grading of gliomas in the World Health Organization classification of brain tumours was originally designed mainly to provide clinicians with guidance as to the natural course of disease and the necessity of further treatment beyond surgery. The profound prognostic impact of this pathological grading has been confirmed over the last decades in numerous retrospective analyses. Yet, it has also become clear that tumours virtually identical by morphology may have very different outcomes and that molecular markers may aid in deriving more detailed prognostic information. The 1p/19q co-deletion in oligodendroglial tumours became paradigmatic in this regard: patients with 1p/19q-deleted tumours derive much more benefit from radiotherapy or chemotherapy than patients with tumours lacking this aberration. Thus, the 1p/19q status does not help to select among different genotoxic treatments. The first molecular marker attributed a predictive power specifically for benefit from alkylating agent chemotherapy was promoter methylation of the O6-methylguanylmethyltransferase gene. However, it now seems that this predictive effect may be limited to glioblastoma and that implementation of the according test in clinical practice is a major challenge. The identification of isocitrate dehydrogenase mutations as typical changes restricted to certain types of gliomas and the rapid development of common mutation-specific antibodies has provided a major advance in subclassifying gliomas, but not resulted in novel treatment strategies yet. A specific type of epidermal growth factor receptor mutation, EGFRVIII, has emerged as a target for vaccination. Ongoing high-throughput analyses are likely to yield novel candidate biomarkers in due course, suggesting that molecular neopathology will have an increasing impact in clinical neurooncology very soon. Eur Assoc of Neuro Oncol Mag 2012; 2 (1): 6–10.

Key words: MRI, DTI-FT, fMRI, neuronavigation, brain mapping, glioma

Introduction

The current World Health Organization (WHO) Classification of Tumours of the Nervous System allows for a histomorphological subtyping of brain tumours and a grading into WHO grades I–IV according to the expected degree of malignancy [1]. One major goal of the WHO classification was to provide clinicians with guidance as to the natural course of disease and the indication to withhold or offer further treatment beyond surgery, specifically radiotherapy or chemotherapy. The profound prognostic impact of the pathological grading afforded by the WHO classification has been confirmed over the last decades in numerous retrospective analyses. Yet, these studies as well as prospective interventional trials have also shown that tumours identical by morphological criteria may have highly different outcomes and that molecular markers may aid in deriving more detailed prognostic information upfront. Numerous such molecular markers in the field of glioma have been explored, many without attracting enduring attention. Some, however, continue to raise interest over years, such as p53 mutations, epidermal growth factor receptor (EGFR) mutations, and the 1p/19q co-deletion, others such as O6-methylguanylmethyltransferase (MGMT) promoter methylation and mutations of isocitrate dehydrogenase (IDH) 1 and B-Raf, are subject of ongoing studies and controversies (Table 1, Figure 1). Moreover, powerful high-throughput analyses, which also led to the identification of IDH as a mutational target [3], are likely to yield novel diagnostic and prognostic information in the very near future. The article at hand summarizes and extends previous reviews on the development of molecular markers for the differential diagnosis and stratified management of gliomas [2, 4–7]. The potential value of molecular markers includes, but is not limited to aid in the differential diagnosis of brain tumours that are at times difficult to distinguish to allow prognostication within tumour entities to allow prediction of response or lack of response to a specific type of treatment.

Notably the distinction between prognostic and predictive molecular factors is not consistently made in the literature and has given rise to controversies and misconceptions, eg, the false assumption that patients with 1p/19q-co-deleted oligodendrogliomas should be treated with chemotherapy or chemotherapy plus radiotherapy rather than radiotherapy alone (see below).

p53

The tumour suppressor protein (TP) 53 acts mainly as a transcription factor that controls the transcription of several genes involved in cell cycle arrest, DNA repair, senescence, and apoptosis, eg, p21 or bax. Mutations of the p53 gene or effectors of the p53 pathway are among the most common molecular aberrations in human cancers. Among gliomas, p53 mutations are relatively common in WHO grade-II and -III tumours and, accordingly, also in secondary glioblastomas, that is, glioblastomas progressing from previously lower-grade gliomas. In contrast, p53 mutations are relatively rare in glioblastoma.

Since p53 controls DNA damage response pathways and is thought to promote either DNA repair and survival or irreversible growth arrest, traditional views held that the p53 status should correlate with responses to radiotherapy or DNA-damaging agent chemotherapy. While this can be nicely modelled in cell culture models and p53 knockout mice, such an asso-
EGFR

Amplification, constitutive activation, or increased expression of the epidermal growth factor receptor (EGFR) gene may promote EGFR-signalling and thereby proliferation, invasiveness, and resistance to cell death induction. EGFR amplification or mutational activation are rare in gliomas of lower WHO grades, but frequent in primary glioblastomas and glioblastoma in elderly patients [9, 10]. EGFR overexpression has been associated with inferior prognosis in some, but not all studies, and a major prognostic impact in glioblastoma can be ruled out. Numerous EGFR-targeted agents, including tyrosine kinase inhibitors such as gefitinib or erlotinib, as well as antibodies have been explored in patients with newly diagnosed or recurrent glioblastoma, but never produced a signal for activity justifying phase-III development. It has been argued that upfront EGFR status determination to enrich patients likely to respond to EGFR-targeted treatments might be necessary to improve the outcome of anti-EGFR trials in glioblastoma. Thus it has been proposed that patients with high EGFR expression and low levels of phosphorylated protein kinase B/Akt respond better to erlotinib than those with low levels of EGFR expression and high levels of phosphorylated protein kinase B/Akt [11]. Furthermore, it was reported that the coexpression of EGFRvIII and phosphatase-and-tensin-homolog-on-chromosome-ten (PTEN) by glioblastoma cells was associated with responsiveness to EGFR kinase inhibitors [12]. However, neither of these observations was confirmed in the prospective randomized European Organization for Research and Treatment of Cancer (EORTC) 26034 trial on erlotinib in recurrent glioblastoma [13]. Since the EGFR status is not strongly prognostic and since no EGFR-targeting agents are approved for glioma treatment, currently there is no need for the determination of EGFR mutation or expression status outside a clinical trial, and its knowledge will not influence clinical decision-making. However, a specific type of EGFR mutation, EGFRvIII, which gives rise to a truncated receptor that is active independent of ligand, produces a neoantigen that might be amenable to immunological targeting [14, 15]. Thus the detection of EGFRvIII might assume relevance at least for inclusion into clinical trials in the next few years.

1p/19q

Combined losses of genetic material from chromosomal arms 1p and 19q, now commonly referred to as 1p/19q co-deletions, result from an unbalanced translocation which leads to the loss of one hybrid chromosome and thereby loss of heterozygosity (LOH) [16]. These observations early on indicated the presence of tumour suppressor genes on 1p or 19q. 1p/19q co-deletions are almost never found in non-glial tumours and are strongly associated with oligodendrogial morphology. In WHO grade-II gliomas, the absence or presence of this biomarker does not correlate with progression-free survival in patients treated by surgery alone, but neither with radiotherapy nor chemotherapy [8, 17]. However, they identify anaplastic glioma patients with a superior outcome independent of whether these patients are treated with radiotherapy or chemotherapy or both [18–20]. In glioblastoma, 1p/19q co-deletions are rare and of unknown biological significance. The higher effectivity of radiotherapy and chemotherapy in oligodendroglioma patients with 1p/19q co-deletions has given rise to the hypothesis that these chromosomal regions harbour not only tumour suppressor genes but also important genes which may determine cellular sensitivity to genotoxic stress or cell death stimuli in general. However, only very recently the first convincing candidate genes have been identified. By means of coding exon sequencing, mutations in 2 genes hitherto not related to gliomas, the CIC gene, a homologue of the drosophila gene capicua), and the FUBP1 gene, which encodes the “far upstream element (FUSE) binding protein” on chromosome 19q, were found in a relevant proportion of oligodendroglial tumours [21]. To what extent mutations in CIC or FUBP1 contribute to oligodendrogliomagenesis or the radiochemosensitivity of 1p/19q-co-deleted oligodendrogliomas is currently under intense investigation.

MGMT

MGMT is a DNA repair enzyme that reverses the alkylation of DNA induced by alkylating agent chemotherapy, including nitrosoureas and temozolomide. The MGMT protein is consumed during this process by its targeting to the proteasome and is therefore often classified as a suicide enzyme. A association of MGMT expression and the efficacy of alkylating agent chemotherapy in glioblastoma has been proposed for more than 20 years [5]. However, most studies reporting a prognostic impact of MGMT in glioblastoma examined promoter methylation of the MGMT promoter rather than protein levels or activity in the tumour cells. In fact, there was generally poor correlation between promoter methylation and loss of protein, and promoter methylation correlated better with outcome than MGMT protein determination by immunohistochemistry [5, 22]. The reasons for these discrepancies may have included poor-quality antibodies or difficulties in distin-
Guiding MGMT-expressing tumour from non-tumour host infiltrating cells. Alternatively, MGMT promoter methylation may not always result in loss of protein expression and may signify a biological feature with significance beyond MGMT, that is, there may be a pattern of gene silencing by methylation that predicts a better outcome [23]. The MGMT promoter methylation status shows little intratumoural heterogeneity [24] and is preserved at recurrence in most glioblastomas [25, 26].

In the context of the pivotal trial that showed the superiority of concomitant and adjuvant temozolomide plus radiotherapy over radiotherapy alone [27], MGMT promoter methylation was strongly associated with the extent of benefit from the addition of chemotherapy in the experimental arm [28], but had only minor prognostic impact on progression-free survival in patients treated with radiotherapy alone. This set of data is currently the only to demonstrate that MGMT promoter methylation is not only an overall prognostic factor, but predictive for benefit of chemotherapy, if only in glioblastoma. The strong prognostic role of MGMT promoter methylation has recently been confirmed in the RTOG 0525/EORTC/NCCTG Intergroup Study that investigated 3 weeks on one week off adjuvant temozolomide dose intensification in comparison with the standard EORTC/NCIC treatment schedule. While there was no difference in progression-free or overall survival, the primary endpoint, between both treatment arms, overall survival was 23.2 months in patients with MGMT promoter-methylated tumours as opposed to 16 months in patients with unmethylated tumours [29]. The PCR-based assay used in that trial is being prepared for commercial use by MDX Health (Ghent, Belgium).

IDH

Somatic mutations of isocitrate dehydrogenase (IDH) genes 1 and 2 have only recently been described, but have already had a major impact in diagnostic neurooncology [3, 7, 30, 31]. The IDH1 gene encodes cytosolic NADP+-dependent IDH whereas the IDH2 gene encodes mitochondrial NADP+-dependent IDH. IDH mutations cluster at codon 132 of the IDH1 respectively codon 172 of the IDH2 gene, suggesting that these mutations afford a gain of function to tumour cells. If merely loss of IDH function was the main mechanism, any type of mutation resulting in loss of functional enzyme would be tumourigenic. Present concepts include that the mutant IDH variants exhibit an altered substrate specificity which results in the production of a putative oncometabolite, D-2-hydroxyglutarate. While this oncometabolite has been considered a possible biomarker to monitor disease activity in acute myeloid leukaemia, the only other cancer with a relatively high rate of IDH mutations, D-2-hydroxyglutarate levels may be too low in the serum of glioma patients to be of diagnostic value [32].

The IDH mutation rate in astrocytic and oligodendrogial gliomas of grades II and III is in the range of 60-80 % whereas the rate does not exceed 10 % in glioblastomas, indicating a differential cellular origin of these tumours. Other brain tumours such as ependymomas lack IDH mutations. This differential distribution and the development of an antibody-recognizing mutant IDH1 R132H protein [33], which accounts for > 90 % of all mutants in gliomas, explains why IDH assessment was rapidly introduced into the diagnostic repertoire of neuropathology in many centres.

Table 1. Molecular markers in glioma: an overview

<table>
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<th>Biological significance</th>
<th>Method of assessment</th>
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<td></td>
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<td>Grade-II gliomas</td>
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<td>p53</td>
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<td>histochemistry</td>
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<tr>
<td>1p/19q</td>
<td>Biological role unclear, co-deletion of chromosomal arms 1p and 19q linked to oligodendrogial morphology</td>
<td>PCR, FISH</td>
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<tr>
<td>MGMT</td>
<td>DNA repair</td>
<td>Methylation-specific PCR</td>
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<tr>
<td>IDH</td>
<td>Biological role unclear, possible link to energy metabolism and pro-angiogenic pathways</td>
<td>PCR or immuno-histochemistry (IDH1R132H)</td>
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<tr>
<td>B-Raf</td>
<td>Cell growth and division</td>
<td>PCR</td>
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</table>
Within glioma entities II–IV, patients with IDH-mutant tumours show a longer survival than patients with IDH-wild-type tumours [20, 34, 35]. Yet, the IDH status, like the 1p/19q status, does not predict benefit from a specific type of treatment, eg, radiotherapy versus chemotherapy [20, 36, 37]. Interestingly, the survival of glioblastoma patients with IDH mutation is superior to that of anaplastic astrocytoma without IDH mutation [38], illustrating that molecular features can profoundly improve the prognostic power of the current, largely morphological neuropathological assessment.

### B-Raf

B-Raf is a member of the Raf kinase family which belongs to the serin threonine kinases and regulates cell growth and division via mitogen-activated protein kinase (MAPK) and extracellular signal-related kinases (ERK). Duplications of B-Raf are frequent in pilocytic astrocytomas [39, 40]. Since B-Raf mutations are rare in diffuse astrocytic gliomas of WHO grades II–IV, their absence or presence may aid in the differential diagnosis of pilocytic and higher-grade astrocytomas. An activating point mutation, B-RafV600E, is found in approximately 60–70% of pleomorphic xanthoastrocytomas and 20% of gangliogliomas, but again very rarely in other types of glioma [41, 42]. The detection of B-Raf pathway activation might assume therapeutic relevance since specific inhibitors of B-Raf, such as PLX-4032, are already explored for efficacy in malignant melanoma. Moreover, less selective multikinase inhibitors such as sorafenib inhibit B-Raf, too. Finally, inhibitors of heat shock protein (HSP) 90, which destabilize mutant B-Raf, may be of interest in this regard.

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**Figure 1.** Molecular markers in glioma. **A,** 1p/19q co-deletion. Microsatellite-PCR-based analysis of allelic losses of 1p and 19q in an astrocytoma (WHO grade II) (A II) and an anaplastic oligodendroglioma (WHO grade III) (AO III). Losses of both markers are indicated by arrowheads in AO III, but not A II. **B,** MGMT promoter methylation. Methylation-specific PCR for unmethylated (U) and methylated (M) promoter sequences in 5 glioblastoma samples, including the glioblastoma cell line A172 as a positive control for methylated and peripheral blood cells as a control for unmethylated promoter sequences, as well as water as a negative control (empty). **C,** IDH mutation. Grade-II oligoastrocytoma, upper panels: HE staining, lower panels: IDH immunostaining, left panels: tumour centre, right panels: infiltration zone (Courtesy: Jörg Felsberg, Düsseldorf, Germany). Reprinted from [2].

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**Is Molecular Neuropathology Ready for Clinical Use?**

Major progress has been made in recent years to supplement the morphological framework of the WHO classification [1] with molecular markers of diagnostic and prognostic significance (Table 1, Figure 1). MGMT promoter methylation stands out as a marker where choice of assay and technical standardization have turned out to be most challenging [5]. EGFR amplification, 1p/19q co-deletion, IDH mutation, and B-Raf alterations are characteristic of specific tumours whereas MGMT promoter methylation is not. 1p/19q co-deletion, IDH mutation, and MGMT promoter methylation are strongly prognostic in anaplastic gliomas. Importantly, these 3 favourable markers may not be independent, eg, the 1p/19q co-deletion lost significance upon the multivariate analysis of the NOA-04 trial when MGMT and IDH status were included in the analysis [20]. Only IDH mutations are confirmed to be prognostic in grade-II gliomas. In glioblastoma, IDH mutations indicate the origin from a prior lower-grade lesion, and MGMT promoter methylation is probably both prognostic and predictive for benefit from alkylating-agent chemotherapy. Accordingly, molecular neuropathology provides a lot of diagnostic and prognostic information, but is still largely dispensable for individual clinical decision-making.

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**Molecular Markers and Clinical Trial Design**

Molecular markers have been introduced into the design of clinical trials to enrich patient populations, that is, to define...
more homogeneous patient populations which are more likely to respond to treatment in a uniform manner. This strategy has been employed for MGMT promoter methylation in the CENTRIC trial for newly diagnosed glioblastoma, based on the analysis of a small phase-II trial [43] and, based on robust historical data [18, 19], for the 1p/19q co-deletion in the multinational CATNON and CODEL trials which are also open in many European countries. As one of the next steps, it seems reasonable to exclude glioblastoma patients with IDH mutations from future glioblastoma trials. The most convincing use of molecular marker analysis would be the analysis of the EGFVR8 mutation in glioblastoma as the requirement for inclusion into a vaccination trial targeting specifically this common type of mutation [15].

Outlook

Further areas of biomarker research that are far less advanced in terms of implementation in the clinic include the diagnostic and prognostic use of glioma stem cell markers as well as the identification of predictive markers for benefit from specific types of antiangiogenic treatment. These could include not only tumor tissue markers but also plasma biomarkers such as vascular endothelial growth factor (VEGF) family members or their soluble receptors [44, 45] or vessel structures amenable to advanced imaging techniques such as integrins expressed on the luminal vessel wall [46].

Conflict of Interest

The author has received research grants from MSD, M erck Serono, and Roche and honoraria for lectures or advisory boards from M agofce, MSD, M erck Serono, and Roche.

References:

Advances in Technology in Radiation Oncology

Mehmet Ufuk Abacioglu

Abstract: The last decade has shown breathtaking developments in radiotherapy. As a local and organ-preserving method, radiation oncology as a discipline is changing its paradigm to more sophisticated, precise treatments rather than large-field irradiations. A radiation beam is more like a scalpel in the era of hypofractionated and ablative doses. It becomes increasingly possible to escalate the fractional and total doses without increasing toxicity; toxicity may even decrease. While early clinical results with these new technologies are very satisfactory, evidence-based long-term results are anticipated. Eur Assoc Neurooncol Mag 2012; 2 (1): 11–4.

Key words: radiotherapy, radiation oncology, neurooncology, radiosurgery

Introduction

For many decades, radiation has been one of the main weapons against tumors located in the central nervous system as well as in many other sites. It has potentially curative and ablative effects not only on malignant tumors but also on benign tumors and vascular malformations. Beginning with the radium and kilovoltage X-rays, technological developments have made radiotherapy an essential component of therapy [1]. While the first revolutionary development were Cobalt machines and linear accelerators to treat deep-seated tumors, there has been an evolution of computer and imaging technologies over the last 30 years. Transition from 2-D treatments to 3-D and nowadays 4-D has been possible with CT, MR, and PET imaging. Irregularly shaped targets can be better irradiated using 3-D conformal and intensity-modulated beams. Stereotactic radiosurgery and radiotherapy have been widely adopted in daily practice with the aim of precise and accurate ablative treatments, making it possible to shorten many treatments and to improve patient comfort. Image guidance during treatment has been an important component for these highly precise techniques. Orthogonal X-rays, in-room CT and cone beam CT are examples for right targeting during treatment.

This review aims to cover recent technological developments of radiotherapy targeting central nervous system (CNS) diseases.

Intensity-Modulated Radiotherapy

With the use of CT, 3-dimensional (3-D) visualization of the patient anatomy has been possible and 3-D-conformal radiotherapy has been widely used in almost any treatment site. It has the advantage of improving dose conformity around the target and of sparing adjacent normal tissues compared to conventional radiotherapy fields. Intensity-modulated radiotherapy (IMRT) is a more sophisticated method to deliver highly conformal radiotherapy and its use has been largely common especially in head, neck, prostate, and brain tumors in proximity to critical structures. The basis for IMRT relies on an inverse-planning system, which optimizes delivery of non-uniform beam fluences from multiple directions to allow the intended dose to reach the target with maximal sparing of normal tissues. The treatment system involves use of multi-leaf collimators that divide each beam into many small beamlets, which are each modulated such that the overall beam intensity patterns achieve the desired target coverage and critical tissue sparing. IMRT treatment for high-grade gliomas has allowed for improved target conformity without increasing the integral dose and volume of normal tissue exposed to low doses of radiation [2].

Helical tomotherapy, developed by Tomotherapy, Inc, as a dedicated rotational IMRT system with a slip-ring rotating gantry, achieves more efficient delivery by continuous gantry rotation and treatment couch translation (Figure 1). It has the advantage of spiral IMRT treatments without the problem of intersecting fields [3].

Linear accelerator vendors have released the capability to vary the angular dose rate by dynamically changing dose rate and/or gantry speed during arc delivery. This new capability, referred to as volumetric-modulated arc therapy (VMAT), has likely spurred a re-emergence of clinical interest in the use of arc therapy. An advantage of VMAT is the potential reduction in delivery time compared with IMRT [4]. A 200-cGy fraction dose can be delivered within 1.5–3 min with VMAT [5]. Varian with RapidArc and Elekta has the commercially available VMAT softwares being used in their linear accelerators.

Figure 1. Novel radiotherapy and radiosurgery platforms: TomoHD Tomotherapy. Image used with permission from Accuray Incorporated.
and treatment planning systems. RapidArc treatment planning and delivery of integrated plans of whole-brain radiotherapy (WBRT) and boosts to multiple brain metastases is a rapid and accurate technique that has a higher conformity index than conventional summation of WBRT and radiosurgery boost [6]. With this technique it is feasible to treat both the macroscopic metastases to a higher dose and the microscopic disease with a lower prophylactic dose at the same time (Figure 2). Another novel technique is hippocampus sparing during whole-brain radiotherapy, aiming at the reduction of neurocognitive complications of whole-brain irradiation [7]. It is possible to reduce the median dose for the hippocampus to 5–8 Gy, while other parts of the brain receive 30 Gy.

With the advent of precise radiation techniques, the role of prophylactic irradiation both in primary brain tumours (like glioblastoma) or metastases has been questioned. Even in the concurrent temozolomide era, local in-field recurrences are still the majority. Recent studies show that a 1-cm clinical target volume expansion to the contrast-enhancing areas might result in the same local recurrence rate as a 2–3-cm margin [8]. For patients with a limited number of metastases, radiosurgery alone results in the same overall survival as with the addition of whole-brain irradiation [9].

The proton beam has a very advantageous physical character. It has a very rapid dose fall-off at the range. However, its dependence on a large particle accelerator, which is very expensive to build, has prevented the technique from being widely used. There is ongoing research by several companies to construct proton machinery with smaller accelerators, and at an affordable price to make this highly conformal treatment accessible to larger populations.

## Stereotactic Radiosurgery and Hypofractionated Radiotherapy

Since Leksell’s conception of stereotactic radiosurgery, technology has proliferated and radiosurgery has become a standard procedure in the treatment of many benign and malignant CNS pathologies [10]. Radiosurgery relies on 3-D or stereotactic image localization, thereby enabling co-identification of a virtual target in the treatment-planning computer with the actual target position for treatment delivery [11]. The first Gamma Knife containing 179 Co-60 sources became operational in Stockholm in 1968. It was redesigned using 201 Co-60 sources arranged in a hemispherical configuration to create a more spherical dose distribution. Treatment is performed by positioning the patient’s tumour in the centre of the focused radiation. Models B and C were developed to facilitate reloading of the Co-60 sources and patient positioning. The Perfexion model has 192 Co-60 sources arranged in a cylindrical configuration in 5 rings (Figure 3) [12]. The new repositioning head frame, “Extend”, facilitates fractionated treatments and extends the treatment fields to the cervical and upper neck regions as well.

Cyberknife is a compact X-band linear accelerator mounted on a 6-axis robotic arm (Figure 4) [13]. The multi-axis robotic arm allows the positioning of the linear accelerator in any direction and at various surface-to-axis distances. With a complex planning process to choose the optimal beam configura-
tions and beam weights, automated procedures help physicians and physicists. Diagnostic X-rays mounted to the ceiling enable real-time orthogonal image guidance without the need for a stereotactic frame. Bony structures or implanted radio-opaque markers allow the localization of the target. The dynamic tracking software, Synchrony, allows to follow the target in moving parts of the body.

In recent years, linac-based radiosurgery manufacturers have also developed high-technology linear accelerators to specifically deliver radiosurgery more accurately and efficiently [14–16]. All of the linacs currently marketed for radiosurgery share common features: higher dose rates, integrated image guidance, integrated high-resolution multi-leaf collimation, and improved mechanical accuracy [11]. The first example was Clinac 600SR by Varian, a dedicated radiosurgery accelerator with a single 6-MV energy with a 10 × 10 cm maximum field size [17]. Later on, Varian’s partnership with BrainLab improved linac-based radiosurgery technology. Besides circular collimators, computer-controlled mMLC® micro-multileaf collimators (mMLC) with a 3-mm projection at the beam isocentre allowed for beam-shaping and intensity-modulated radiosurgery. Image guidance on the Novalis systems is performed by the fully integrated ExacTrac X-Ray 6D, which consists of 2 infrared cameras for patient prepositioning and tracking, 2 floor-mounted X-ray tubes, and 2 ceiling-mounted amorphous silicon flat panel detectors for X-ray image guidance. These components allow for computer-assisted infrared and X-ray-based correction and verification of the patient’s position before and during treatment. Varian has extended the radiosurgery partnership to Trilogy and Novalis TX high-energy linear accelerators which are also equipped with cone beam CT, allowing for the acquisition of soft-tissue imaging for image guidance. Similarly, both Elekta and Siemens have marketed radiosurgery linacs featuring higher dose rates, higher accuracy, high-resolution mM LCs, and CBCT for soft-tissue image guidance (Figure 5).

Traditional radiosurgery uses an invasive headring for stereotactic localization and minimization of motion during image acquisition and treatment. Taking into account the disadvantages of frame-based invasive systems, several frameless systems have been developed. They rely on optical and/or image guidance. Thermoplastic masks are used for immobilization. Extracranial radiosurgery (eg, of the spine) has also become an effective and more frequently used treatment to increase the effectiveness of radiation treatment for tumours in close proximity to very critical structures such as the spinal cord.

In recent years, there has been increasing interest in flattening filter-free (FFF) linacs [18]. It is possible to expect a reduction in the out-of-field dose due to reduced head scatter and residual electron contamination, which results in a benefit for normal tissues because of decreased scatter doses [19]. Removal of the flattening filter may also provide delivery of the dose up to 4 times faster. Besides its treatment efficiency, radiobiological implications of increased dose rates are investigated [20]. The first commercially available system is TrueBeam from Varian. A further integration of the TrueBeam linac with the Novalis ExacTrac imaging and positioning system, a 6-dimensional couch and high-definition multi-leaf collimators were added to further improve the precision of radiosurgery and SBRT (Figure 6).

As a result of these flexible platforms for any type of radiotherapy, it has been possible to use different fractionation
regimens from multiple fractions to single-fraction treatments. Large tumours in the brain that cannot be irradiated in a single fraction now have the option to be irradiated with hypofractionated treatments. Using the accurate imaging, it has been possible for some tumours to shorten overall treatment time by means of hypofractionation.

Image-Guided Radiotherapy

Detailed anatomical imaging in CNS has been one of the most important milestones for treatment of CNS tumours. Revolution change has been made by the implementation of 3-dimensional imaging with soft tissue visualization of the body by CT and MR. Modern treatment planning softwares have the capability of registering and fusing MR and CT image sets, which significantly enhances the accuracy of target delineation [21]. A monocaid and hypoxia tracers for PET/CT, besides new MR techniques like diffusion, perfusion, and spectroscopy, have added metabolic information to the anatomical delineation [22]. They are useful for target delineation, dose-painting, and evaluation of disease progression. A thorough investigation at the moment, delineation of nerve fibre tracts and shape of dose according to this information allow for the radiation oncologist to decrease the possible complications of radiotherapy, just like its use in neuro-oncology [23].

A potential source of inaccuracies in the treatment of patients relates to the difficulty in daily repositioning of the patient within the immobilization device in exactly the same way [21]. Image-guided radiotherapy (IGRT) is visualization of the target and the normal structures just before and during treatment and correction of the potential set-up errors. Different vendors have different on-board imaging (OBI) solutions for image guidance. Orthogonally paired X-ray images can be compared to the digitally reconstructed radiographs (DRR) which are created from the simulation CT to check the set-up accuracy and to correct positioning errors. One beam CTs, integrated to the modern linacs, make it possible to image the soft tissues in-room and correct positioning according to the verification of registered images with the planning CT scan.

For extracranial treatments, respiratory motion is an important component of intrafractional motion. 4-D CT simulation makes it possible to have images at different phases of respiration and to contour the target and critical structures separately. Gating, active breath control, and tracking are contemporary methods, both to increase the accuracy of treatment and to decrease the volume and dose applied to critical structures.

Conclusions

Radiotherapy is an important part of the standard of care for many CNS tumours. Recent technological advances have enhanced our targeting accuracy, thereby reducing unnecessary, so far normal tissue doses. New technologies have also provided the possibility to shorten the fractional and overall treatment times, which is an improvement regarding patient comfort and quality of life. Integration of systemic and targeted therapies with novel radiotherapy technologies is investigated for their synergistic interactions.

Conflict of Interest

M UA has no conflict of interest to declare.

References:
Spectrum of Side Effects of Anticonvulsants in Patients with Brain Tumours

Christa P Bénit, Charles J Vecht

Abstract: Seizures are a common manifestation in patients with brain tumours, and most patients need anticonvulsants. Apart from seizure control, the risk of side effects makes the proper choice of anticonvulsants a major concern. Toxicities not only exist as common side effects, but also appear as drug-drug interactions, neurotoxicities, and other organ dysfunctions.

One reason for interactions is the use of the classical anti-epileptic drugs (AED), phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ). Large differences in dose regimens with concomitant chemotherapy reflect the potency of these effects. Although valproic acid (VPA) can be beneficial to prevent tumour growth, it may lead to bone marrow suppression and other toxicities because of its enzyme-inhibiting properties.

Another noteworthy side effect are skin reactions, like erythema multiforme, which occasionally develops during radiation. Although this side effect is rare, it can be life-threatening. Many anti-epileptic drugs can have extra toxic effects with existing organ dysfunction, like bone-marrow suppression or liver abnormalities, this applies particularly for PB, PHT, CBZ, and VPA.

Existing clinical or subclinical signs of brain damage secondary to space-occupying tumoural effects or the sequelae of previous neurosurgery, radio-, and chemotherapy enhance the chances of neurotoxicity. Besides, the intake of anticonvulsants itself and their total number strongly contribute to cognitive dysfunction. As neurocognitive decline interferes with quality of life, such changes may substantially affect daily activities of patients and their family members.

The multitude of co-therapies applied with brain tumours contributes to a myriad of side effects that are almost impossible to unravel, as drugs and other therapies used can have aggravating or counteracting effects on each other. Knowledge of individual anticonvulsants and anticipation of toxicity including the recognition of already existing co-morbidities all contribute to better selection and dosing of anticonvulsants, including the choice of agents that do not interact. Although this survey is not aimed at the proper drug choice, future studies need to show which anti-epileptic agents or combinations would be the best match to achieve effective seizure control together with good tolerability.

Key words: brain tumour, seizure, anticonvulsant, drug interaction, toxicity, cognitive dysfunction

Introduction

Epilepsy is common in patients with brain tumours, and seizures constitute the presenting symptom in 30–50% of patients with brain tumours [1]. Seizures can also affect patients with systemic cancer with brain or leptomeningeal metastases or by organ dysfunction or drug treatment, including chemotherapy causing metabolic or toxic encephalopathies [2]. For these reasons, patients with seizures and cancer often need anticonvulsants; 1/3 of patients with primary brain tumours use AEDs [3]. Unavoidably, this may lead to side effects either as general toxic effects, or more specifically related to the underlying condition, for example the occurrence of interactions with concomitantly administered chemotherapeutic agents. In this review, we will comment on the general side effects of anticonvulsants, followed by a more extensive discussion on side effects of anticonvulsants associated with brain tumours or systemic cancer.

Seizures in patients with brain tumours can be classified as partial (simple or complex partial) or symptomatic, with or without secondary generalisation. Here we briefly mention the main characteristics of anticonvulsants, and Table 1 depicts an overview of the main mechanisms of action, the metabolic pathways involved, their pharmacokinetic properties and common toxicities, including idiosyncratic side effects occurring in cancer patients.

Phenobarbital (PB) is one of the oldest anticonvulsants and still in use in many parts of the world. Major drawbacks are its relatively strong sedating effect as well as its being a strong enzyme-inducer. Nevertheless, because of its action as a broad-spectrum anticonvulsant, it may still be applied in treatment-resistant seizures. In cancer patients, one should be aware of cognitive side effects, hepatic dysfunction, skin reactions including Stevens-Johnson syndrome (SJS), and drug interactions.

Phenytoin (PHT) is a first-generation anticonvulsant which is also employed in status epilepticus. It is a strong enzyme-inducer and has been implied in many reports on interactions with co-administered agents, including chemotherapeutic drugs (CTD). Besides, it shows non-linear pharmacokinetics and has a relatively small therapeutic window. Today, it is mainly applied by the intravenous route in status epilepticus, and is felt to be less suitable for oral maintenance therapy. Interaction with other drugs and side effects like encephalopathy, hepatitis, coagulation defects, and bone marrow hypoplasia are of concern in patients with brain tumours.

Carbamazepine (CBZ) is a still widely used first-generation anticonvulsant for partial seizures. It is a potent enzyme-inducer and can strongly accelerate the metabolism of many
Table 1. Mechanisms of action of AEDs (in alphabetical order) and pharmacokinetic characteristics. Based on [5–8].

<table>
<thead>
<tr>
<th>AED</th>
<th>Usual dosage (mg/day)</th>
<th>Therapeutic range (mg/l)</th>
<th>Common/important side effects</th>
<th>Main mechanism of action</th>
<th>Oral bio-availability (%)</th>
<th>Time to peak levels (h)</th>
<th>Metabolism and excretion</th>
<th>Vₘ (l/kg)</th>
<th>T₁/₂ (h)</th>
<th>CL (l/kg/h)</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>400–1600</td>
<td>4–12</td>
<td>Leukopenia, aplastic anaemia, hepatotoxicity, hyponatraemia, SJS/TEN</td>
<td>Blocks voltage-dependent Na⁺-channels</td>
<td>75–85</td>
<td>4–8</td>
<td>Hepatic epoxidation, conjugation</td>
<td>0.8–2</td>
<td>5–26</td>
<td>0.133</td>
<td>75</td>
</tr>
<tr>
<td>CZP</td>
<td>0.5–4</td>
<td>0.02–0.08</td>
<td>Sedation, cognitive effects, drowsiness</td>
<td>GABA receptor agonist</td>
<td>90</td>
<td>1–4</td>
<td>Hepatic reduction and acetylation</td>
<td>1.5–4.4</td>
<td>20–60</td>
<td>0.09</td>
<td>86</td>
</tr>
<tr>
<td>FBM</td>
<td>1200–3600</td>
<td>30–100</td>
<td>Hepatic disturbance, SJS aplastic anaemia, insomnia, weight loss</td>
<td>NMDA and Na⁺-channel conductance &gt; 90</td>
<td>2–6</td>
<td>Hepatic hydroxylation and conjugation (60 %), renal excretion (40 %)</td>
<td>0.75</td>
<td>13–30</td>
<td>0.027–0.032</td>
<td>20–25</td>
<td></td>
</tr>
<tr>
<td>GBP</td>
<td>900–3600</td>
<td>2–20</td>
<td>Weight gain, worsening of seizures</td>
<td>Blocks Ca²⁺-channels, GABA receptor agonist &lt; 65</td>
<td>2–3</td>
<td>Renal excretion without metabolism</td>
<td>0.65–1.04</td>
<td>5–7</td>
<td>0.120–0.130</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>LCM</td>
<td>200–400</td>
<td>10–20</td>
<td>Dizziness, headache, nausea, diplopia, blurred vision, cognitive dysfunction, skin reactions</td>
<td>Slow inactivation of voltage-dependent Na⁺-channels &gt; 95</td>
<td>2–4</td>
<td>Hepatic demethylation, unchanged renal excretion (40 %)</td>
<td>0.6</td>
<td>13</td>
<td>&lt; 15</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>200–600</td>
<td>1–15</td>
<td>Rash, SJS, TEN, DRESS, headache, blood dyscrasia, ataxia</td>
<td>Blocks voltage-dependent Na⁺-channels &gt; 95</td>
<td>1–3</td>
<td>Hepatic glucuronidation (without phase-1 reaction), renal excretion (10 %)</td>
<td>1.0–1.3</td>
<td>12–60</td>
<td>0.044–0.084</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>LEV</td>
<td>1000–3000</td>
<td>3–30</td>
<td>Somnolence, asthenia, irritability, psychosis</td>
<td>Binding to synaptic vesicle protein 2 (VSV2A) &gt; 95</td>
<td>0.6–1.3</td>
<td>Partially hydrolysed in the blood, 0.5–0.7</td>
<td>5–11</td>
<td>0.01</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>900–2400</td>
<td>10–35</td>
<td>Somnolence, headache, diplopia, SJS, bone marrow suppression, hyponatraemia</td>
<td>Blocks voltage-dependent Na⁺-channels &gt; 95</td>
<td>4–6</td>
<td>Hydroxylation, glucuronidation</td>
<td>0.3–0.8</td>
<td>8–10</td>
<td>38</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>30–180</td>
<td>15–40</td>
<td>Rash, hepatotoxicity, impaired cognition, ataxia, mood change, SJS/TEN</td>
<td>GABA receptor agonist, glutamate antagonist, blocks voltage-dependent Na⁺-Ca²⁺-channels 80–100</td>
<td>1–3</td>
<td>Hepatic oxidation, glucosidation, hydroxylation, conjugation</td>
<td>0.42–0.75</td>
<td>46–136</td>
<td>0.006–0.009</td>
<td>45–60</td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>150–400</td>
<td>10–20</td>
<td>Blood dyscrasia, hepatitis, SJS, gum hyperplasia, lupus-like reactions, hirsutism</td>
<td>Blocks voltage-dependent Na⁺-channels &gt; 95</td>
<td>4–12</td>
<td>Hepatic oxidation, hydroxylation, conjugation</td>
<td>0.5–0.8</td>
<td>24–72</td>
<td>0.003–0.02</td>
<td>85–95</td>
<td></td>
</tr>
<tr>
<td>PGB</td>
<td>150–600</td>
<td>2–8</td>
<td>Somnolence, dizziness, ataxia</td>
<td>Binds to Ca²⁺-channels</td>
<td>90</td>
<td>1</td>
<td>No metabolism, renal excretion</td>
<td>6.3</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TPM</td>
<td>100–500</td>
<td>2–20</td>
<td>Impaired cognition, hepatotoxicity, weight loss, renal calculi</td>
<td>Blocks Na⁺-channels, GABA receptor agonist, blocks NMDA receptors 81–95</td>
<td>2–4</td>
<td>No metabolism, mainly renal excretion</td>
<td>0.6–1.0</td>
<td>19–25</td>
<td>0.022–0.036</td>
<td>9–17</td>
<td></td>
</tr>
<tr>
<td>VGB</td>
<td>200–300</td>
<td>0.8–36</td>
<td>Visual field defects (33 %, often irreversible), fatigue, drowsiness</td>
<td>GABA transaminase inhibitor</td>
<td>80–90</td>
<td>1–2</td>
<td>No metabolism, renal excretion (70 %, unchanged)</td>
<td>0.8</td>
<td>6–8</td>
<td>Similar to GFR</td>
<td>None</td>
</tr>
<tr>
<td>VPA</td>
<td>500–2500</td>
<td>50–100</td>
<td>Hepatotoxicity, thrombo- and neutropenia, aplastic anaemia, tremor, weight gain, hair loss, ovarian cystic syndrome</td>
<td>Uncertain, may affect GABA glutamnergic activity &gt; 95</td>
<td>1–10</td>
<td>Hepatic glucuronidation, oxidation, conjugation</td>
<td>0.15</td>
<td>8–15</td>
<td>0.006–0.015</td>
<td>85–95</td>
<td></td>
</tr>
<tr>
<td>ZON</td>
<td>200–600</td>
<td>20–30</td>
<td>Somnolence, ataxia, dizziness, renal failure</td>
<td>Blocks Na⁺- and Ca²⁺-channels &gt; 95</td>
<td>2–6</td>
<td>Hepatic acetylation, glucuronidation (30 %), renal excretion (30 %)</td>
<td>1.2–1.8</td>
<td>60–70</td>
<td>0.015–0.019</td>
<td>40–50</td>
<td></td>
</tr>
</tbody>
</table>

**AED**: antiepileptic drug; Vₘ: volume of distribution; T₁/₂: elimination half-life; CL: clearance; DRESS: drug reactions with eosinophilia and systemic symptoms; Na⁺: sodium; NMDA: N-Methyl-D-aspartate; Ca²⁺: calcium; K⁺: potassium; GFR: glomerular filtration rate; CBZ: carbamazepine; CZP: clonazepam; FBM: felbamate; GBP: gabapentin; LCM: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbitone; PHT: phenytoin; PGB: pregabalin; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; TPM: topiramate; VGB: vigabatrin; VPA: valproic acid; ZON: zonisamide.
other drugs. Relevant side effects include drug interactions, hepatotoxicity, skin reactions including Stevens-Johnson syndrome (SJS), leukopenia, bone marrow dyscrasia, and hyponatraemia.

Valproic acid (VPA) is a broad-spectrum anticonvulsant for both generalized and partial epilepsy with rather mild toxicity. Recent reports indicate that it may also have anti-tumour effects in glioblastoma multiforme and other types of cancer, possibly secondary to its action as a histone-deacetylase inhibitor [9–11]. In children and adults with high serum levels, one should be aware of a disturbed haemostasis; monitoring of liver functions, platelet counts, and coagulation parameters is advisable. The impact of these abnormalities is uncertain as clinical studies have not indicated enhanced bleeding tendencies following neurosurgery. Nevertheless, in patients with cancer, one should be aware of drug-drug interactions and side effects including hepatotoxicity, disturbed haemostasis, bone marrow suppression, and skin reactions, i.e., rash, SJS, or toxic epidermal necrolysis (TEN).

Clonazepam (CZP) is a benzodiazepine, and a broad-spectrum and effective anticonvulsant. Because its use may easily lead to sedation and tolerance, its application is generally restricted to the abrogation of acute seizures, in status epilepticus, or as a last resort therapy when other antiepileptic drugs have failed.

Lamotrigine (LTG) represents a first-choice anticonvulsant for symptomatic partial epilepsy. However, although lamotrigine by itself has only weak inducing and inhibiting activities of the P-450 co-enzyme system of the liver, LTG is susceptible to induction by concomitantly given drugs. A drawback of lamotrigine is that the initiation of therapy requires a long time period of dose increments before therapeutic ranges are reached. One should be aware of side effects in cancer patients such as skin reactions (SJS, TEN), bone marrow toxicity, and drug interactions.

Oxcarbazepine (OXC) has a close structural similarity to CBZ but it is better tolerated and shows fewer drug interactions. In patients with cancer, one should be aware of hyponatraemia, skin reactions (SJS, TEN), and sometimes bone marrow suppression.

Topiramate (TPM) is a second-generation and effective broad-spectrum AED with no obvious drug interactions, although its tolerability is lower than for many of the other newer AEDs. In cancer patients, one should be aware of cognitive dysfunction, hepatic abnormalities, and blood dyscrasia (rare).

Gabapentin (GBP) is one of the second-generation anticonvulsants, it is generally well-tolerated and shows no interaction with other drugs. However, it has a limited efficacy and sometimes a worsening of seizures may happen. In patients with renal dysfunction, dose adjustment is necessary.

Felbamate (FBM) can lead to serious adverse events, like hepatic abnormalities or aplastic anaemia; its use is mainly restricted to intractable types of epilepsy.

Levetiracetam (LEV) has good anti-seizure efficacy, including in brain tumours [12–15]. Its major advantage is the absence of interactions with other agents. It is being excreted by the kidney, and in the presence of renal dysfunction, dose adjustment is necessary. Side effects include irritability and psychosis; blood dyscrasia is rare.

Pregabalin (PGB) is a third-generation anticonvulsant that does not show pharmacokinetic interactions with enzyme-inducing or -inhibiting drugs. To date, there is little experience with pregabalin as an anticonvulsant, including its application in brain tumour patients. In patients with renal dysfunction, dose adjustment is necessary.

Lacosamide (LCM) selectively enhances slow sodium channel inactivation. Because of the absence of drug interactions, lacosamide seems a promising AED in cancer. Presently, it is registered for use as an add-on AED. Side effects include cognitive dysfunction and skin reactions.

Zonisamide (ZON) is a broad-spectrum anticonvulsant and is metabolised by conjugation with glucuronic acid. It does not inhibit or induce hepatic co-enzymes, however, other enzyme-inducing drugs, like PHT and PHB, can enhance its metabolism. Side effects like weight loss and cognitive disturbances are of concern in patients with brain tumours.

### Drug Interactions

Drug interactions are characterized as either pharmacokinetic (when uptake, distribution, metabolism, or excretion is affected) or pharmacodynamic (when target organs or receptor sites are affected). Pharmacokinetic drug-drug interaction occurs when ≥ 2 drugs are administered simultaneously and one drug modifies the metabolism of the other. In this way, serum concentrations of co-administered drugs can become reduced or elevated, leading to either ineffective therapy or drug toxicity. The most common interactions between antiepileptic and cytostatic drugs are of a pharmacokinetic nature, and as a rule may occur when both are being metabolized by a corresponding co-enzyme of the P450 CYP system, by epoxide oxidation, or by glucuronidation in the liver [16, 17]. Although the CYP system consists of approximately 60 different isoenzymes, 5 of them (CYPs 3A4, 2D6, 2C9, 2C19, and 1A2) are responsible for the metabolism of 95% of all drugs, of which the CYPs 3A4, 2C9, and 2C19 (Table 2) are particularly important in relation to potential interactions of AEDs [19, 20]. An overview of the different groups of chemotherapeutic agents and the interactions they may have with anticonvulsants, most notably with enzyme-inducing AEDs, is given in Table 3.

### Compromised Activity of CTDs by Enzyme-Inducing AEDs

#### Alkylating Agents

Cyclophosphamide is an alkylating agent and is commonly administered in the treatment of malignant lymphomas, leukaemias, neuroblastoma, retinoblastomas, and carcinomas of the ovary, breast, endometrium, and lung, usually in combination with other chemotherapeutic drugs [25]. By itself, cyclophosphamide is inactive and requires enzymatic bioactiv-
Spectrum of Side Effects of Anticonvulsants in Patients with Brain Tumours

Table 2. Mechanisms of metabolism of AEDs and their effects on the P450 hepatic CYP system. Based on [16, 18].

<table>
<thead>
<tr>
<th>AED</th>
<th>Metabolism</th>
<th>Substrate (CYP)</th>
<th>Inducer (CYP)</th>
<th>Inhibitor (CYP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>Cytochrome P450</td>
<td>1A2, 2C9, 2C19, 3A4</td>
<td>1A2 (s), 2B6 (s), 2C9 (s), 2C19 (s), 3A4 (s)</td>
<td>3A4 (s)</td>
</tr>
<tr>
<td>CZP</td>
<td>Cytochrome P450</td>
<td>3A4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FBM</td>
<td>Cytochrome P450</td>
<td>2E1</td>
<td>2C19, 3A4 (w)</td>
<td>2C19</td>
</tr>
<tr>
<td>GBP</td>
<td>Not metabolised</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LCM</td>
<td>Partial cytochrome P450</td>
<td>2C19</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LTG</td>
<td>UDPGT glucuronidation</td>
<td>–</td>
<td>UDGPT (w)</td>
<td>–</td>
</tr>
<tr>
<td>LEV</td>
<td>Non-hepatic hydrolysis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>OXC</td>
<td>UDPGT glucuronidation, limited</td>
<td>–</td>
<td>2C19 (w), 3A4 (w)</td>
<td>2C19 (w)</td>
</tr>
<tr>
<td></td>
<td>cytochrome P450 metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>Cytochrome P450</td>
<td>2C9, 2C19, 2E1</td>
<td>1A2 (s), 2B6 (s), 2C8 (s), 2C9/2C19 (s), 3A4 (s)</td>
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</tr>
<tr>
<td>PHT</td>
<td>Cytochrome P450</td>
<td>2C8, 2C9, 2C19</td>
<td>1A2, 2B6 (s), 2C9/19 (s), 3A4 (s)</td>
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<tr>
<td>PGB</td>
<td>Not metabolised</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TPM</td>
<td>Mainly renal excretion, limited</td>
<td>–</td>
<td>2C19 (w), 3A4 (w)</td>
<td>2C19 (w)</td>
</tr>
<tr>
<td></td>
<td>cytochrome P450 metabolism, UDPGT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>glucuronidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VGB</td>
<td>Not metabolised</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>VPA</td>
<td>Cytochrome P450, UDPGT</td>
<td>2A6, 2B6, 2C9, 2C19</td>
<td>–</td>
<td>2C9, EH, UDGPT</td>
</tr>
<tr>
<td></td>
<td>glucuronidation, β-oxidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZON</td>
<td>Cytochrome P450</td>
<td>2C19, 3A4, 3A5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AEDs: see Table 1; s: strong; w: weak; CYP: cytochrome P450 enzyme; UDPGT: uridine diphosphate glucuronyltransferase

Antimetabolites
Methotrexate is an antimetabolite that acts as a folate antagonist, it is widely applied in different types of cancer, including leukaemia, lymphomas, and breast cancer. Methotrexate inhibits dihydrofolate reductase, leading to reduced synthesis of DNA, RNA, and proteins [67]. Its elimination is mainly renal, and 80–90 % is unchanged excreted in urine [68]. In a retrospective study, 40 of 716 children with acute lymphoblastic leukaemia receiving PB, PHT, or CBZ had a lower plasma clearance of methotrexate and teniposide, together with a worse event-free survival, more haematological and CNS relapses, and a shorter survival [26]. In a small retrospective study, blood levels of methotrexate were lower in patients receiving EIAEDs as compared to either the non-EIAED topiramate or not receiving any anticonvulsant [27]. The exact mechanism of interaction between the AEDs methotrexate and EIAEDs is not known.

Topo-Isomerase Inhibitors
Etoposide and teniposide are used in non-small-cell lung carcinoma (NSCLC) and acute myeloid leukaemia, (non-) Hodgkin’s lymphoma, acute lymphoblastic leukaemia, and in autologous bone marrow transplantation, and are mainly metabolized by CYP 3A4 [64]. The Cl of etoposide is about 77 % faster in patients on concomitantly administered EIAEDs [38]. Concomitant use of PB or PTH leads to a 2–3-fold increase of Cl of teniposide, which may thus compromise its efficacy [37]. The camptothecin analogue topotecan is mostly used in refractory small-cell lung cancer and ovarian cancer, and co-administration of PHT leads to a 47 -% increase of Cl and fewer haematological side effects [69]. For 9-aminocamptotecin, plasma concentration levels are 3× lower with concomi-
Co-medication with EIAEDs results in an increase in clearance of 27–57 % and a decrease in bioavailability of 75 % of irinotecan [28].

Other Cytostatic Drugs
Ixabepilone is a novel microtubule-targeting agent with antitumour activity against ovarian, colon, cervical, gastric, breast, melanoma, NSCLC, and non-Hodgkin’s lymphoma. Together with EIAEDs, the MTD is 41 % and the CI 50 % higher, probably by induction of 3A4 [70].

Proteinkinase Inhibitors
Research into the development of gliomas and other carcinomas has improved the understanding of specific cellular, molecular, and genetic mechanisms that lead to cancer growth and progression. To date, many agents can target these pathways, including tyrosine-kinase inhibitors and angiogenic inhibitors. The metabolism of these drugs is often influenced by concomitant administration of anticonvulsants.

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) and is used in NSCLC, and mainly metabolized via the iso-enzymes 3A4, 3A5, and to a lesser extent by 1A2 [47]. The MTD for erlotinib is 200 mg/day without enzyme induction and more than 2–3× higher (450–650 mg/day) together with an EIAED [42, 43].

Another tyrosine-kinase inhibitor is the small molecule gefitinib that is used in NSCLC and is metabolized by 3A4, 3A5 co-enzymes, and the non-inducible CY P2D6. For patients using an EIAED, the peak dose of gefitinib is –45 %, the AUC –60 % and the MTD 4× higher (1000 mg/d) as com-

<table>
<thead>
<tr>
<th>Group CTD</th>
<th>Type of CTD</th>
<th>AED that reduces CTD</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Busulphan</td>
<td>PHT</td>
<td>Cl 15 % ↑, AUC 16 % ↓, T1/2 23 % ↓</td>
<td>[21]**</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>PB, PHT</td>
<td>AUC 67 % ↓, biotransformation 200–300 % ↑</td>
<td>[22]** [23]**</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>PHT</td>
<td>AUC ↓ (ns), CI ↑ (ns)</td>
<td>[24]**</td>
<td></td>
</tr>
<tr>
<td>Thiopeta</td>
<td>PHT</td>
<td>AUC 29 % ↓</td>
<td>[25]**</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate</td>
<td>PB, PHT, CBZ</td>
<td>CI ↑ (ns), Cmax 90 % ↓</td>
<td>[26]** [27]**</td>
</tr>
<tr>
<td>Antimitotic agents</td>
<td>9-Amino-camptotecin</td>
<td>PB, PHT, CBZ</td>
<td>Cmax 67 % ↓, MTD 109 % ↑, CI 122 % ↑</td>
<td>[28]** [29]**</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>PB, PHT, CBZ, PRM, OXC</td>
<td>MTD 160–250 % ↑, CI 61 % ↑</td>
<td>[30]** [31]** [32]**</td>
</tr>
<tr>
<td></td>
<td>Topotecan</td>
<td>PHT</td>
<td>CI 47 % ↑</td>
<td>[33]**</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>EIAEDs (ns)</td>
<td>MTD 43–57 % ↑, MTD 50 % ↑, Cmax 55 % ↓</td>
<td>[34]** [35]** [36]**</td>
</tr>
<tr>
<td></td>
<td>Teniposide</td>
<td>PB, PHT</td>
<td>CI 146 % ↑</td>
<td>[37]**</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>AEDs (ns)</td>
<td>CI 77 % ↑</td>
<td>[38]**</td>
</tr>
<tr>
<td>Proteinkinase inhibitors</td>
<td>Erlotinib</td>
<td>EIAEDs (ns)</td>
<td>Cl 47 % ↑</td>
<td>[40]**</td>
</tr>
<tr>
<td></td>
<td>Enzastaurin</td>
<td>EIAEDs (ns)</td>
<td>Cmax 80 % ↓</td>
<td>[41]**</td>
</tr>
<tr>
<td></td>
<td>Gephitinib</td>
<td>PB, PHT, CBZ, PRM, OXC</td>
<td>AUC 60 % ↓, MTD 300 % ↑</td>
<td>[42]** [43]**</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>PHT, CBZ, PRM, OXC, TPM</td>
<td>Cmax 66–88 % ↓, MTD 50 % ↑</td>
<td>[44]**</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>EIAEDs (ns)</td>
<td>Cmax ↓</td>
<td>[45]** [46]**</td>
</tr>
<tr>
<td></td>
<td>Tipifarnib</td>
<td>PB, PHT, CBZ</td>
<td>AUC 83 % ↓, MTD 100 % ↑</td>
<td>[47]**</td>
</tr>
<tr>
<td></td>
<td>Vatalanib</td>
<td>PB, PHT, CBZ, PRM, OXC</td>
<td>Cl 200 % ↑, Cmax 67 % ↓</td>
<td>[48]**</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus</td>
<td>PB, PHT, CBZ, OXC</td>
<td>Cmax 73 % ↓, MTD 47 % ↑, Cmax 33 % ↓</td>
<td>[50]** [51]**</td>
</tr>
<tr>
<td></td>
<td>Sirolimus</td>
<td>PB, PHT, CBZ, OXC</td>
<td>AUC 39 % ↓, MTD 100 % ↑</td>
<td>[52]** [53]**</td>
</tr>
<tr>
<td></td>
<td>Everolimus</td>
<td>EIAEDs (ns)</td>
<td>Lower C (ns)</td>
<td>[54]** [55]**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CTD</th>
<th>AED that increases toxicity of CTD</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCNU (Lomustine)</td>
<td>VPA</td>
<td>Frequency of haematological toxicity 60 % ↑</td>
<td>[9]** ***</td>
</tr>
<tr>
<td>AED</td>
<td>CTD that increase toxicity of AED</td>
<td>Effect</td>
<td>Reference</td>
</tr>
<tr>
<td>PHT</td>
<td>5-Fluorouracil</td>
<td>Cmax (PHT) 170–225 % ↑</td>
<td>[54]** [55]**</td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td>Cmax (PHT) 168–171 % ↑</td>
<td>[56]** [56]**</td>
</tr>
<tr>
<td></td>
<td>Doxifluoridine</td>
<td>Cmax (PHT) 400 %</td>
<td>[57]**</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>Cmax (PHT) 322–406 % ↑</td>
<td>[58]**</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>Cmax (PHT) 44 %</td>
<td>[59]**</td>
</tr>
<tr>
<td>VPA</td>
<td>Fotemustine/Cisplatin</td>
<td>Frequency of haematological toxicity 300 % ↑</td>
<td>[60]** ***</td>
</tr>
<tr>
<td>PHT, PB, CBZ, VPA (as combination therapy)</td>
<td>Procarbazine</td>
<td>Frequency of skin hypersensitivity reactions 390 % ↑</td>
<td>[61]** ***</td>
</tr>
</tbody>
</table>

CTD: chemotherapeutic drug; AED: antiepileptic drug (abbreviations: see Table 1); Cl: clearance; AUC: area-under-the-concentration-time curve; T1/2: elimination half-life; ns: not specified; C: concentration; EIAED: enzyme-inducing antiepileptic drug; Cmax: plasma concentration; MTD: maximum tolerated dose; PRM: primidone; TD: tolerated dose; Csteady-state concentration; Cmax: peak plasma concentration. case report (1–4 patients); ** small series (4–19 patients); *** large series (20–49 patients); **** large prospective series (> 50 patients).
pared to an MTD of 250 mg/day without EIAEDs [44]. Imatinib, another selective inhibitor of tyrosine-kinase, is administered in chronic myeloid leukaemia and with gastrointestinal stromal tumours, and largely metabolized by CYP3A4 [46]. Mean trough levels of imatinib are 2.9× lower with an MTD of 1200 mg/day for patients on EIAEDs as compared to 800 mg/day normally [45, 46]. For sorafenib, which is mostly used in advanced renal cell carcinoma and hepatocellular carcinoma, the peak concentration (Cmax) is −54 % and the AUC −63 % for patients on EIAEDs [47].

Tipifarnib is currently under investigation, mostly in blood and breast cancers. A phase-I trial of tipifarnib in patients with recurrent glioma using EIAEDs showed that the MTD is 2× higher, and the AUC approximately 2× lower than for patients not on EIAEDs. It is unclear to what extent either glucuronidation or oxidative metabolism by P450 co-enzymes is responsible for this decrease in systemic exposure [48].

Bortezomib is applied in multiple myeloma and in recurrent mantle-cell lymphoma. The use of EIAEDs can lead to an acceleration of metabolism requiring 2× higher doses of bortezomib [40].

In enzastaurin, a VEGFR inhibitor, which is investigated in B-cell lymphoma, chronic lymphatic leukaemia, and solid tumours including glioblastoma, simultaneous EIAED use leads to approximately −80 % AUC [41].

Temsirolimus is an ester of the immunosuppressive agent sirolimus and inhibits the mammalian target of rapamycin. It is mainly used in metastatic renal cell carcinoma and under investigation in glioblastoma multiforme. Sirolimus is an immunosuppressant agent mostly given to transplant patients, and may have anti-tumour activity against malignant gliomas [53]. Both temsirolimus and sirolimus constitute substrates of iso-enzymes 3A4/5. In one study, the peak concentration of temsirolimus was −73 % and of sirolimus −47 % and the AUC −50 % with EIAED co-therapy. Grade-3 haematological toxicity was more commonly seen (20 vs 3 %) in patients on non-EIAEDs [50, 53]. Also, everolimus concentrations are lower with concomitant 3A4-4-inducing AEDs [71].

Increased Toxicity by AEDs or CTDs

Increased toxicity of AEDs may occur when enzyme-inhibiting CTDs are concurrently prescribed. Toxicity of PHT has been observed when combined with S-fluourouracil, tamoxifen, capecitabine, erlotinib, or doxifluridine [55, 57–59]. The underlying mechanism of these interactions is probably a competitive inhibition of PTH clearance by 2C9 and 2C19 iso-enzymes. The use of the alkylating agent procarbazine in combination with PB, PHT, CBZ, or VPA can lead to hypersensitivity reactions of the skin. In a fotemustine-cisplatin regimen, the use of VPA leads to a 4-fold increase of thrombopenia, neutropenia, or both [60].

Corticosteroids

Glucocorticosteroids are frequently used in patients with brain tumours and systemic cancer, their administration can cause drug-drug interactions because of enzyme-inducing effects on the 3A4 iso-enzyme [72]. Vice versa, they are susceptible to agents affecting 3A4; PB, PHT, and CBZ enhance the clearance of dexamethasone 2–4× [5, 73, 74]. Hydrocortisone is metabolized via the hepatic 11-B-hydroxysteroid dehydrogenase system, which is also susceptible to enzyme induction. PB, PHT, and CBZ induce the metabolism of prednisolone with enhanced clearances of 79 %, 41 % and 77 %, respectively, and the metabolism of methylprednisolone more than 3.4, 1.5, and 2×, respectively [75]. Vice versa, dexamethasone given together with PHT may lead to an increased clearance of PHT and therefore with a lesser anti-epileptic activity. Increased seizure frequency has indeed been observed with co-therapy of dexamethasone with 38–50 % lower serum PHT levels [76–78]. When dexamethasone is discontinued, PHT concentrations can easily rise to toxic levels [79].

These observations emphasize that it is equally important to apply dose adjustment not only at the time of initiating medication but also when interacting co-therapy is discontinued. However, also increased levels of PHT have been observed with co-medication of dexamethasone. Apparently, the use of dexamethasone can lead to unpredictable interactions with PHT, including either enzyme-inducing or -inhibiting effects.

From these observations, one may conclude that simultaneous use of enzyme-inducing anticonvulsants and corticosteroids should rather be avoided, or, when given simultaneously, that plasma concentrations of anti-convulsants should be monitored.

Idiosyncratic and Skin Reactions

Bone marrow suppression and liver dysfunction can occur as a side effect of a number of individual AEDs, and are more frequently seen in association with brain tumours than with other co-morbidities [4]. This can be explained by overlapping adverse events of CTDs, which are often more pronounced with the concomitant use of AEDs. For example, haematotoxicity can be the result of administration of PB, PHT, CBZ, or VPA, but is also common with use of temozolomide and other chemotherapy agents [80, 81].

Also, severe systemic allergic reactions can occur with the use of a number of AEDs, mainly at the time of initiation of therapy with PB, PHT, CBZ, OXC, VPA, or LTG [82]. The most common type of hypersensitivity is skin rash as a side effect of AEDs, which can be accompanied by fever, lymphadenopathy, and, occasionally, by multi-organ abnormalities [83]. Its frequency seems higher in patients carrying a brain tumour than in non-tumoural patients with epilepsy [84, 85]. More severe allergic reactions are erythema multiforme or the Stevens-Johnson syndrome and toxic epidermal necrolysis with necrosis and blistering of skin and mucosal membranes, which may lead to a potential mortality of up to 40 % [86]. A number of observations strongly suggests an increased appearance of SJS in patients undergoing cranial irradiation and receiving anticonvulsants, particularly with PB, PHT, or CBZ, often together with co-therapy with glucocorticosteroids [87, 88]. Nevertheless, the appearance of this severe dermatological complication is relatively rare. In one retrospective review of 289 patients receiving radiotherapy and anticonvul-
Cognition

Besides pharmacokinetic effects, antiepileptic drugs can also influence cognitive functioning. The conventional anticonvulsants PB, PHT, CBZ, and VPA are all associated with cognitive side effects showing impairments in memory, mental speed, and attention with a less favourable cognitive profile of PB as compared to other anticonvulsants [93–95]. Although these side effects are mild or moderate [93], their impact can be substantial if patients already suffer from cognitive dysfunction due to space-occupying effects of the tumour or by the sequelae of neurosurgery, radio-, and chemotherapy [96]. A neurocognitive decline interferes with quality of life, such changes may have great impact on the daily life of patients and family members [97].

In a group of 156 long-time survivors of low-grade gliomas, a higher seizure frequency was associated with mental deterioration. The use of one of the conventional anticonvulsants led to a worse performance in 6 out of 7 cognitive domains [98]. Particularly, an inverse relationship was observed between anti-epileptic polytherapy with AEDs, i.e., the number of anticonvulsants taken simultaneously had an unfavourable effect on executive and psychomotor functioning in patients with low-grade gliomas and hypothalamic hamartomas [98–100].

In general, the newer AEDs like GBP, LTG, OXC, PGB, and LEV confer less pronounced cognitive side effects, with the exception of TPM (Table 4) [105–107]. A retrospective study comparing TPM (n = 429), LTG (n = 336), and LEV (n = 301) in non-brain tumour-related epilepsy showed that almost half of the patients using TPM discontinued its use because of mental slowing in 27.8 % and dysphasia in 15 % [101, 108]. At the same time, almost 10 % of patients on LTG experienced positive cognitive effects like improved alertness, better emotional stability, or less irritability [108, 109]. In a study on 70 patients with gliomas, patients on one of the conventional AEDs suffered from more adverse events than those on OXC (42.9 % vs 11.4 %) and psychomotor slowness was only seen with the traditional AEDs (21.7 %) [102]. In another study on 40 patients with seizures and gliomas, switching to levetiracetam monotherapy showed no negative effects on 6 domains of cognition. LEV might even have positive effects as there were no signs of cognitive decline despite the presence of a brain tumour or administration of ancillary anti-tumour therapy [104]. Two smaller observational studies (including 11 and 29 patients, respectively) showed mild cognitive impairment, it is unclear whether this is caused by the disease (i.e., tumour progression) or by the use of LEV [14, 103].

Conclusion

Today, patients with brain tumours undergo intensive therapy, including neurosurgery, radiation therapy, and chemotherapy, at various stages of the disease. Besides, the majority of patients needs anticonvulsants to control epileptic seizures, and often glucocorticosteroids or other ancillary therapies to control symptoms secondary to tumoural effects or to anti-tumour therapy. For these reasons, this multitude of co-treatments easily leads to a myriad of side effects in patients with brain tumours, drugs used simultaneously may either aggravate or counteract each other. The use of anticonvulsant drugs illustrates each of these situations, thus—apart from seizure control—a lot of attention is needed for avoiding or neutralizing these side effects in patients with brain tumours. Obviously, the first issue in prescribing anticonvulsants is to take into account pharmacokinetic properties and common side effects (Table 1). A nother point of attention is the issue of recognition of interactions with chemotherapy due to the enzyme-inducing or -inhibiting effects of conventional AEDs (Table 2). The substantial effect that enzyme-inducing AEDs can have on the treatment of brain tumours is reflected by the large differences of dose regimens of chemotherapeutic agents, depending on whether or not patients receive an enzyme-inducing AED. Prospective phase-I/II trials on CTDs divided in strata with or without EIAEDs have produced corresponding data on drug clearance, area-under-the-curve values, and median or maximum tolerated doses of new cancer agents, and illustrate the strong enzyme-inducing capabilities of phenobarbital, phenytoin, and carbamazepine (Table 3). Nevertheless, these effects are not so easily detected as they are mainly manifested by a potential inefficacy of chemotherapeutic or targeted drugs on the underlying tumour. As many types of brain tumours including low- and high-grade gliomas or systemic cancers often become resistant to anti-tumour-directed therapy, a poor response to therapy is easily accounted for by ineffective therapy rather than by co-treatment with an enzyme-inducing agent. Likewise, chemotherapeutic agents themselves often have enzyme-inducing or -inhibiting properties leading to either potential inefficacy or toxicity of antiepileptic drugs.

By making use of pharmacokinetic data on drug interactions (Tables 2, 3), one may argue that potential adverse interactions can be prevented by a timely dose adjustment according to the anticipated effect of these interactions. To do so reliably, this will require therapeutic drug monitoring of the applied chemotherapy as well as anticipating and accounting for a dose amendment at each change of the AED regimen. To what extent this approach is indeed feasible in daily practise is uncertain, as medical oncologists taking care of cancer treatment not seldom work in other hospitals than neurologists prescribing and monitoring anticonvulsants. In practice, this makes proper adjustment of medication difficult to pursue or even elusive. Probably, the risks of harmful interactions take place on a much larger scale than we assume, as physicians probably often do not realise or are unaware of the possibility of interactions.

Obviously, the use of anticonvulsants may lead to interactions not only with chemotherapeutic agents, but also with many
Spectrum of Side Effects of Anticonvulsants in Patients with Brain Tumours

Other kinds of drugs, for many other conditions or co-morbidities, which may accompany patients with brain tumours. One noteworthy side effect is the occurrence of severe dermatological complications, which is the result of an intricate interaction between anticonvulsants and the administration of cranial radiotherapy, possibly related to co-medication with steroids and expression of certain HLA alleles.

Apart from interactions, many anticonvulsants have side effects that can be extra damaging in patients already at risk for organ dysfunction like bone marrow suppression or liver dysfunction. Compared to the second- and third-generation anticonvulsants, the use of conventional anticonvulsants PB, PHT, and CBZ more often leads to hepatic dysfunction and, to a lesser extent, also to bone marrow suppression.

Lastly, also the risk on neurotoxicity is of major importance in patients with brain tumours and seizures, as both the need for anticonvulsants and the number of anticonvulsants used are each stronger contributing factors to the severity of cognitive dysfunction than having gone through earlier neurosurgical excision or radiation therapy (Table 4). Although reviewing satisfactory seizure control is beyond the scope of this paper, the risk of ineffective cancer treatment, organ dysfunction, and neurotoxicity illustrates the importance of effective and well-tolerated anticonvulsants that do not interfere with cancer treatment. Fortunately, there is a number of anticonvulsants that possess these properties. Oxcarbazepine, lamotrigine, and topiramate have only weak enzyme-inducing or -inhibiting properties. Although valproic acid can have enzyme-inhibiting activity and can lead to hepatic dysfunction and thrombopenia, its histone-deacetylase-inhibiting activity may help to control tumour progression. Lastly, gabapentin, levetiracetam, pregabalin, and lacosami-

<table>
<thead>
<tr>
<th>AED</th>
<th>Number of patients</th>
<th>Type of study</th>
<th>Tumour diagnosis</th>
<th>Method of cognitive function assessment</th>
<th>Mean follow-up (months)</th>
<th>Main drawbacks of study</th>
<th>Cognitive side effects</th>
<th>Main drawbacks of study</th>
<th>Cognitive side effects</th>
</tr>
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<tr>
<td>TMP</td>
<td>33</td>
<td>Observational</td>
<td>LGG, GBM, MEN, MBT</td>
<td>Clinical notes, hospital charts</td>
<td>13.7</td>
<td>Retrospective assessment of cognitive functioning</td>
<td>Severe dermatological complications</td>
<td>Severe dermatological complications</td>
<td>Severe dermatological complications</td>
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<tr>
<td>OXC</td>
<td>36</td>
<td>Observational retrospective</td>
<td>LGG, OXCI</td>
<td>MMSE</td>
<td>8.1</td>
<td>Clinical notes, hospital charts</td>
<td>Severe dermatological complications</td>
<td>Severe dermatological complications</td>
<td>Severe dermatological complications</td>
</tr>
<tr>
<td>LEV</td>
<td>29</td>
<td>Prospective follow-up</td>
<td>LGG, AA, GBM, MEN, MBT</td>
<td>LEV monotherapy, patients served as their own controls</td>
<td>11</td>
<td>LEV monotherapy, patients served as their own controls</td>
<td>No differences in neuropsychological assessed sub-sequent follow-up measurements</td>
<td>No differences in neuropsychological assessed sub-sequent follow-up measurements</td>
<td>No differences in neuropsychological assessed sub-sequent follow-up measurements</td>
</tr>
</tbody>
</table>

**Table 4.** Cognitive side effects of AEDs in patients with brain tumours

- AED: antiepileptic drug (abbreviations see Table 1).
- AA: anaplastic astrocytoma.
- AO: anaplastic oligodendroglioma.
- GBM: glioblastoma multiforme.
- HGG: high-grade glioma.
- LGG: low-grade glioma.
- MBT: metastatic brain tumour.
- MEN: meningioma.
- VPA: valproic acid.
- OXC: oxcarbazepine.
- LEV: levetiracetam.
- PTX: phenytoin.
- PHT: phenobarbital.
- TPM: topiramate.
- BB: benzodiazepines.
References:
20. Gidal BE. Drug absorption in the elderly: spec- trum of Side Effects of Anticonvulsants in Patients with Brain Tumours


Chemotherapy and Polyneuropathies

Wolfgang Grisold1, Stefan Oberndorfer2, Anthony J Windebank3

Abstract: Peripheral neuropathies induced by chemotherapy (CIPN) are an increasingly frequent problem. Contrary to haematologic side effects, which can be treated with haematopoetic growth factors, neither prophylaxis nor specific treatment is available, and only symptomatic treatment can be offered.

CIPN are predominantly sensory, duration-of-treatment-dependent neuropathies, which develop after a typical cumulative dose. Rarely motor, autonomic, or CNS involvement occurs. Typically, the appearance of CIPN is dose-dependent although in at least 2 drugs (oxaliplatin and taxanes) immediate effects can appear, caused by different mechanisms. The substances that most frequently cause CIPN are vinca alkaloids, taxanes, platin derivates, bortezomib, and thalidomide. Little is known about synergistic neurotoxicity caused by previously given chemotherapies, or concomitant chemotherapies. The role of pre-existent neuropathies on the development of a CIPN is generally assumed, but not clear.

Neurologists are often called in as consultants for cancer patients suffering from CIPN and have to assess whether the neuropathy is likely to be caused by chemotherapy or other mechanisms, whether treatment needs to be modified or stopped due to CIPN, and what symptomatic treatment should be recommended.

Possible new approaches for the management of CIPN could be genetic susceptibility, as there are some promising advances with vinca alkaloids and taxanes. Eur Assoc Neurooncol Mag 2012; 2 (1): 25–36.

Key words: chemotherapy, neurotoxicity, central nervous system, prevention, therapy

Introduction

Patients with oncological diseases need to receive the most effective anti-cancer therapy. To achieve this, usually a combination of surgery, radiotherapy (RT), and chemotherapy, also with biologicals with an increased use of targeted therapies, is applied. Like most other side effects of therapy, such as nausea, haematotoxicity can be managed but the increased use of neurotoxic drugs and the development of CIPN are becoming major dose-limiting factors.

Although the biological effects of all neurotoxic substance classes are known, the precise mode of action on the peripheral nerves is not always clear, and much effort has to be made to develop strategies of prevention and treatment of CIPN. The morphologic correlates of CIPN are depicted in Figure 1. This is of particular importance as the number of long-term survivors has increased due to the success of oncologic treatments and peripheral neurotoxicity becomes a major dose-limiting factor. Patients can be exposed to dysfunctions impairing their quality of life as well as to neuropathic pain. To overcome this challenge several approaches are being made.

Several possibilities for common pathways and affected structures of sensory neurons and peripheral nerves are being discussed. The impairment of mitochondrial function (suggested by the loss of mitochondrial mobility in bortezomib, paclitaxel, and vinca alkaloid neuropathy) could be one of the key factors. Mitochondrial failure could be a mechanism causing axonal injury either by a failure to maintain ionic concentrations, or by the fact that impaired mitochondrial motility results in mitochondria being unable to move to areas of high calcium concentration in the axon, resulting in axonal damage. Mitochondria in aged persons could also be a factor in distal axonal degeneration.

Sensory neurons in the dorsal root ganglia (DRG) seem to be exposed to several pathologies:

- The blood supply of the DRG by fenestrated capillaries that allow passage of drugs into the extracellular space around DRG neurons (blood-nerve-barrier less well-expressed).
- Platinum binding to nuclear DNA appears to stimulate apoptosis.
- The acute toxicity of oxaliplatin occurs at the neuromuscular transmission site (NMT), the acute toxicity of oxaliplatin occurs. Unmyelinated fibers and terminal nerve arbors are the sites of acute neurotoxicity as in platinum compounds. Axons, rarely the myelin, can be damaged. At the neuromuscular transmission site (NMT), the acute toxicity of oxaliplatin occurs. Unmyelinated fibers and terminal nerve arbors are the sites of acute neurotoxicity.
- At the neuromuscular transmission site (NMT), the acute toxicity of oxaliplatin occurs. Unmyelinated fibers and terminal nerve arbors are the sites of acute neurotoxicity.
- Cutaneous sensory fibres lose their glial ensheathment as they approach the epidermis and are less protected contrary to motor fibres.

Figure 1. Morphologic correlates of CIPN. The DRGs can be the target of cumulative neurotoxicity as in platinum compounds. Axons, rarely the myelin, can be damaged. At the neuromuscular transmission site (NMT), the acute toxicity of oxaliplatin occurs. Unmyelinated fibers and terminal nerve arbors are the sites of acute neurotoxicity. An additional spinal mechanism at the alpha-2-delta-Typ1 subunit in neurogenic pain is assumed.
Concerning the severity and expression of neuropathies, as well as the frequency of occurrence, there are major problems. The characterization with scales and scores is heterogeneous and is discussed by Cavaletti et al in this issue [1]. The frequency of neuropathy for each drug is even more complex, as most series rely on small studies or are the result of larger medical oncologic studies which report neuropathies only as side effects. Often, these figures provide no information on associated diseases, pre-existing neuropathies, previous drug treatments, and the combination of chemotherapies. Websites recording individually reported side effects reach large numbers, and by and large they seem to list the distribution of toxic effects, but are not sufficiently evaluated to determine neurotoxic effects. Several reviews on chemotherapy-induced neuropathies exist, which rely on the available data [2–6].

Symptoms, Signs, and Investigations

Clinical Symptoms

Most chemotherapy-induced neuropathies are sensory. As the CIPNs are duration-of-treatment-dependent, tingling or numbness in the feet or fingers is an early sign. Patients also report hypaesthesias, dyseaesthesias or paraesthesiaes and neuropathic pain. Sensory symptoms such as numbness are usually irritating. But also a “plus” of symptoms, such as tingling, itching, stabbing, or pain, may occur. When symptoms progress, the sensory zone widens and progresses from the tips of the extremities to a stocking-glove-like distribution. At this stage, patients are usually already disabled: on the upper extremities by a loss of dexterity and development of clumsiness, on the lower extremities by an addition of instability, resulting in intestinal symptoms, even ileus, and have also been noted in taxanes and platinum compounds.

Muscle symptoms can occur as mononeuropathies or cranial nerve lesions in vinca alkaloids.

Some drugs cause muscle involvement (Table 1) with myalgia, muscle cramps, or weakness [3, 7]. This can be a proximal myopathy as seen in taxanes [8, 9] and vincristine [10]. Myalgia has been observed in a combination of taxanes and gemcitabine [11]. Cramps rarely occur, but when they do, they occur in particular in small foot and hand muscles. The radiation recall syndrome [12] has been described in gemcitabine and carboplatinum. Rhabdomyolysis has been rarely attributed to chemotherapy [13, 14]. Sarcopenia, which is a common phenomenon in advanced cancer, has also been related to drug treatment [15]. In myelomas, muscle amyloidosis occurs as well [16, 17], which is characterized by a combination of weakness and pseudohypertrophic muscles.

Nerve Conduction Velocities (NCV)

Nerve conduction velocity and EMG are the standard tests in clinical neurophysiology. In CIP, NCV usually shows axonal changes often focused on sensory nerves. There is a correlation in axonal neuropathies with the NCV. The clinical correlation, however, has several caveats:

- The correlation is weaker in drugs affecting the DRG, such as platinum derivates, and also in small fibre type changes.
- The correlation is poor with regard to temporal changes within therapy.
- In the clinical situation, the classical examination with a history and findings is more significant than the NCV results. The role of imaging of peripheral nerves in CIPN, such as magnetic resonance techniques and nerve ultrasound, has not been determined.

There are some reports of mononeuropathies occurring with vinca alkaloids and CTS with aromatase inhibitors. For these lesions, it is suggested to use the common NCV criteria.

Skin Biopsy

The role of skin biopsy in CIPN is currently evolving [18]. There are several reports describing small-fibre changes, in

<table>
<thead>
<tr>
<th>Table 1. Muscle symptoms related to chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Proximal weakness</td>
</tr>
<tr>
<td>Radiation recall phenomenon</td>
</tr>
<tr>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Distal cramps</td>
</tr>
</tbody>
</table>

loss of stereotactile recognition of small fibers such as coins, keys etc.

Motor function is usually not an issue in CIPN, apart from vinca alkaloids, which can induce monoparathes and drop foot, and suramin which has a significant motor involvement but is infrequently used.

A utonomic signs are rare but can be seen in vinca alkaloids, resulting in intestinal symptoms, even ileus, and have also been noted in taxanes and platinum compounds.

Table 1. Muscle symptoms related to chemotherapy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis</td>
<td>Cytarabine</td>
</tr>
<tr>
<td>Proximal weakness</td>
<td>Taxanes</td>
</tr>
<tr>
<td>Radiation recall phenomenon</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Necrotizing myopathy</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Taxanes, gemcitabine, several others</td>
</tr>
<tr>
<td>Distal cramps</td>
<td>Vinca alkaloids (as neuropathy)</td>
</tr>
</tbody>
</table>

Muscle symptoms related to chemotherapy (Table 1) with myalgia, muscle cramps, or weakness [3, 7]. This can be a proximal myopathy as seen in taxanes [8, 9] and vincristine [10]. Myalgia has been observed in a combination of taxanes and gemcitabine [11]. Cramps rarely occur, but when they do, they occur in particular in small foot and hand muscles. The radiation recall syndrome [12] has been described in gemcitabine and carboplatinum. Rhabdomyolysis has been rarely attributed to chemotherapy [13, 14]. Sarcopenia, which is a common phenomenon in advanced cancer, has also been related to drug treatment [15]. In myelomas, muscle amyloidosis occurs as well [16, 17], which is characterized by a combination of weakness and pseudohypertrophic muscles.
particular in taxane-related neuropathies. Punch skin biopsies are classified as a minimally invasive procedure. Although loss of nerve fibre density is an end-stage phenomenon in neuropathy, early changes and hopefully future markers may allow to identify prognostic factors. As yet, it can be classified as investigational in CIPN.

### Nerve Biopsy

Although most knowledge of the character of morphological changes in CIPN derives from morphological studies, whole biopsies for CIPN are not indicated unless a differential diagnosis is required to rule out inflammatory, vasculitic, neoplastic, or amyloid neuropathy. Another exception is a biopsy within a defined and approved study protocol.

#### Clinical Course and Development

Most CIPN are dose-dependent neuropathies, with the cumulative dose (Table 2) varying to some extent intraindividually. Usually, at the onset of chemotherapy throughout the first 1–3 cycles, CIPN symptoms appear. From cycle 3–4, usually symptoms develop. In some drugs, it has been observed that after a peak of neurotoxicity the increment of CIPN slows after the 4th or 5th cycle [19, 20]. Due to the length-dependent mechanism, the feet are usually affected first.

#### General Phenomena

Two drugs can produce an immediate toxicity, even after the first dose: (1) oxaliplatin, which has been studied extensively; its CIPN is caused by channelopathy-like mechanisms. (2) A cute, painful small-fibre lesions have been described in taxanes, which are attributed to mitochondrial and small-fibre changes [21].

Once CIPN has developed and the patient suffers from symptoms, the question is usually whether cessation or replacement of the drug is compatible with the oncologic strategy. In this setting, there are 2 other important aspects:

- **Coasting**
  Coasting is an irritating phenomenon. It has been noted particularly with platinum compounds; even after cessation of the neuropathy symptoms can progress and there is a considerable time lag until improvement. Coasting can continue for a few weeks to months. Coasting has also been observed in vinca alkaloids [22] but does not seem to be a frequent phenomenon in this drug.

- **Prognosis**
  The reversibility of CIPN is of increasing importance since active chemotherapies prolong survival. Although there are few long-term studies it must be assumed that CIPN is not always completely reversible. A study with taxanes has shown that even after several months to years some symptoms remain. This is important information in the consultation with patients.

#### Other Influential Factors

- **Pre-existing Neuropathies**
  The influence of pre-existing neuropathies deriving from diabetes mellitus, alcohol abuse, or from a pre-existing hereditary neuropathy on the development of CIPN is considerable. In older patients, also a small percentage of chronic idiopathic axonal neuropathies occurs. Commonly, it is assumed that pre-existing neuropathies, and in particular hereditary neuropathies, may predict a worse course of a neuropathy. In hereditary neuropathies, even devastating effects have been observed in patients receiving chemotherapy.

- **Prior chemotherapy**
  Prior chemotherapy and combinations of chemotherapies are also an issue, especially since patients often receive second- or third-line therapies, also with varying drug combinations [23].

#### Table 2. Cumulative doses. The cumulative dose per square metre is known for several drugs. For many drugs, large series are available. Acute side effects occur only in 2 drugs, other particular effects are mentioned in “other effects.”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cumulative dose</th>
<th>Large series</th>
<th>Acute effects</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>300–400 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>600 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Painful</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>800 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>?</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Addition: cranial nerve mono-neuropathies, autonomic symptoms, necrotizing myopathy</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>?</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Myalgia, myopathy</td>
</tr>
<tr>
<td>Vincristine</td>
<td>5–15 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Painful, rarely demyelinating</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>200 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>400–600 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Painful</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1–1.3 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>20 g (total)</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>?</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>?</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
<tr>
<td>Vincristine</td>
<td>5–15 mg/m²</td>
<td>+</td>
<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
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</tr>
<tr>
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<td>Acute toxicity</td>
<td>Coasting</td>
</tr>
</tbody>
</table>

For the clinical assessment, it has been agreed that the general toxicity scales used in general oncology are too imprecise for the assessment of CIPN. On the other hand, more complex neurologic scales, such as the TNS, are too complicated and
Chemotherapy and Polyneuropathies
time-consuming for non-neurologists, in particular medical oncologists [6, 24–27]. In clinical practice, it would be helpful for oncologists to have a small, easily applicable scale that helps to identify patients with symptoms of neuropathy as early as possible [19, 20]. Several scores are available such as the NCI-CTC [24], ECOG [28], Ajani score, TNS [29], and the modified TNS (sTNS). Patient observations and descriptions are increasingly used and differ from the physicians’ observation. The frequently used numeric rating scales are based on an ordinal setting, where differences amounting to one or two points can actually have dissimilar clinical significance. The CI-PeriNoms Study [30, 31] is an ongoing clinimetric study, which incorporates disability measures, validates quality-of-life scales, and neurophysiological testing to ascertain a better assessment of CIPN. An overview by Cavaletti and the PeriNoms study group depicting this approach can be found in this issue [1].

Substance Groups

1. Alkylators
2. Antibiotics
3. Antimetabolites
4. Mitotic spindle inhibitors
5. Topoisomerase inhibitors
6. Proteasome inhibitors
7. Others
8. Biologicals

Alkylators

Platin Derivates

Three members of the drug family are currently used: cisplatin, carboplatin (mainly in lung, breast, and ovarian cancers), and oxaliplatin (in metastatic colon cancer and undergoing clinical trials for the treatment of other gastrointestinal tract malignancies).

The chemotherapeutic mechanism of platinum compounds is similar to DNA-binding alkylating agents. If the DNA damage exceeds the ability to cell repair, the cell undergoes apoptotic cell death. Platinum compounds induce aberrant re-entry into the cell cycle and apoptosis [32]. Platinum compounds have a unique effect on neurons. Selective vulnerability of DRG-sensory neurons depends presumably on the structure of the blood-nerve-barrier [33, 34]. Also binding of platinum to mitochondrial DNA has been considered a potential mechanism of cell death [35]. Cell death of the sensory neuron results in permanent distal sensory loss.

Clinical Features

Each of the compounds produces dose-dependent sensory symptoms and a sensory neuropathy in relation to the cumulative dose.

Cisplatin

For cisplatin, the development of neuropathies is closely related to the total cumulative drug dose [36, 37]. In the majority of patients who receive >400–500 mg/m² of cisplatin in typically 3–6 months [38, 39], the neuropathy is predominantly sensory with initial complaints of paraesthesias in the distal parts of the extremities. Although all sensory modalities are involved, a loss of large-fibre sensory function is prominent, which often results in sensory ataxia. Lhermitte’s phenomenon is common and probably an expression of spinal cord involvement. Coasting is a unique feature in cisplatin, but can also be observed after spinal radiation. M any patients experience residual pain after some improvement in their neuropathy. This may last for several years after discontinuation of the therapy and should be treated with standard approaches for the management of neuropathic pain.

Motor involvement is rare, however, autonomic neuropathy is infrequent and can cause dizziness, palpitations, or impotence [40].

Retreatment after previous cisplatin chemotherapy does not seem to be complicated by increased neurotoxicity [41].

Laboratory Studies

Electrophysiological features for platinum compounds are mostly axonal changes with a predominance of sensory fibres. Other laboratory studies are not informative. Nerve biopsy studies have shown a loss of large myelinated fibres [42]. A typical constellation of clinical and electrophysiological findings is presented in Figure 2.

Prognosis and Treatment

Neuropathic symptoms can progress up to 2 months after cessation of therapy ("coasting"). Then, gradual improvement may set in. However, because of the underlying pathology

Figure 2. Cisplatinum neuropathy. Clinical and electrophysiological features of a 40-year-old male with an ataxic cisplatinum neuropathy. (a) Despite numbness and sensory ataxia no motor involvement with normal small-hand muscles. Nerve conduction velocity (NCV) measurement shows normal motor NCV. (b) The sensory NCV is reduced to 1 uV (pathologic). (c) The feet appear normal, neither atrophy nor trophic changes can be seen. (d) Knee-to-shin is pathologic, vibration perception is absent. (e) Motor NCVs of peroneal nerves are normal. The sural nerve sensory potential is absent. (f) the F wave is normal.
being a ganglionopathy, recovery may be incomplete, especially in more severe cases.

**Carboplatin**
Carboplatin is less neurotoxic [43]. In higher cumulative doses, however, carboplatin also produces a sensory neuropathy, as does cisplatin [44]. In combination with paclitaxel, 20% of patients develop moderate or severe sensory neuropathies [45].

**Oxaliplatin**
In addition to dose-dependent neuropathies, about 60–80% of patients develop a cold-induced acute toxicity that involves paraesthesias in the throat, mouth, face, and hands occurring within 30–60 min after application and also includes muscle cramps and fasciculations.

The sensations are described as a tingling or burning induced by contact with cold surfaces or cold liquids. They appear acutely and typically remit a few days after the infusion is completed. Also, EMG-spontaneous activity has been observed during the attacks [46].

Oxaliplatin affects voltage-gated sodium channels and interferes with axonal ion conductance [47]. Oxaliplatin is transformed into oxalate, which is an intracellular calcium chelator, which produces similar effects as seen in ethylene glycol poisoning [48]. Oxalate, which is released intracellularly by oxaliplatin, chelates calcium and has an effect on inward sodium channels [49–51]. Divalent cations modify voltage-gated sodium channels [52]. Based on this mechanism, iv calcium gluconate and magnesium sulfate lower acute oxaliplatin symptoms [53].

Cumulative toxicity resembles cisplatin-induced neuropathies. Long-term use demonstrates that oxaliplatin is associated with mild, sensory, and motor axon loss [54]. Oxcarbazepine has been shown to be effective in prophylaxis [55].

**Platinum Hypersensitivity**
In addition to neurotoxicity, other hypersensitivity reactions such as skin rash, flush, abdominal cramps, itching in the palms, and severe cardiovascular reactions have been observed [56]. Usually, these will not be confused with neurotoxicity, except for itching and pruritus.

**Other Alkylating Agents**
Other alkylating agents, such as nitrosoureas, procarbazine, and thiopeta, rarely cause neuropathies, except for ifosfamide.

**Ifosfamide**
Neuropathy occurs in about 8% of patients [57–59]. The onset is gradual, with paraesthesias and pain in the feet. The type of sensory loss is pannmodal. Pre-existent neuropathies are risk factors [60]. Neuropathic pain can be an issue; tendon reflexes are reduced; weakness is rare. Recovery after termination of treatment is slow.

**Procarbazine**
Procarbazine is widely used in haematological malignancies and in the treatment of brain tumours. Mild peripheral neuropathy has been described but is rarely problematic [61]. Myalgias have also been described.

**Thiotepa**
Thiotepa is an alkylating agent occasionally used to treat leptomeningeal metastases. Rarely, intrathecal thiopeta causes a myelopathy [62]. A motor neuropathy has also been described after intrathecal thiopeta chemotherapy [63]. On the whole, this is based on single observations and cannot be generalized.

**Cytotoxic Antibiotics**
Several antibiotics have antineoplastic effects. The most prominent is doxorubicin, which is widely used in several chemotherapies. Although doxorubicin can induce DRG changes in animals, this is not an issue in clinical practice.

Other antibiotics, such as actinomycine, anthracyclines, daunorubicine, valrubicine, idarubicine, epirubicine, bleomycine, plicamycine, and mitamycine, rarely cause peripheral neurologic complications.

**Antimetabolites**
Antimetabolites are compounds which inhibit the synthesis of key intermediary metabolites. Often, they are enzyme inhibitors and may block RNA or DNA synthesis. Most of the anti-metabolites are either analogues of nucleotide bases or interfere with folic acid metabolism. They are more commonly associated with central rather than peripheral neurotoxicity. CINP is generally not a major side effect.

**M ethotrexate**
Methotrexate (MTX) is a folate antagonist that inhibits dihydrofolarate reductase, a key enzyme in the synthesis of nucleotides. It is used alone or in combination chemotherapy for solid tumours and haematological malignancies in a broad spectrum of dosages (low-to-high dose) and also timings (acute as well as permanent therapies). Peripheral neurotoxicity is rare. Although IT treatment is a routine procedure it can be associated with complications, spinal arachnitis, and myelopathy.

Nelarabine is an analogue [64, 65] which does not seem to be involved in the development of CIPN.

**Cytosine Arabinoside**
Cytosine arabinoside (Ara-C) is a pyrimidine antagonist that blocks synthesis of cytosine, thymidine, and uridine. Peripheral neurotoxicity is rare. There are several case reports of various neuropathies associated with the use of high-dose Ara-C [66] and fludarabine combined with Ara-C [67]. These are only observational reports and the clinical relevance is not clear.

Depot Ara-C preparations (depocyte) are increasingly advocated for patients with meningeval carcinomatosis. Recent reports suggest that the drug may cause a cauda equina syndrome [68, 69] in some patients. Repetitive IT drug application with cytarabine treatment caused demyelination in the thoracal roots, the cauda equina, and damage to the posterior columns in a patient treated by the author (Figure 3).
The "hand-foot syndrome", or "palmar plantar erythrodysaesthesias", has been observed in up to 10% of patients. The "hand-foot syndrome", or "palmar plantar erythrodysaesthesias", seem to appear rarely [73, 74].

Capecitabine is metabolized to 5-FU. Except for observations from single cases [72], CIPN are unlikely. Cranial nerve lesions seem to appear rarely [73, 74].

The hand-foot syndrome appears in particular when treatment consisting of 5-FU and capecitabine is applied.

Gemcitabine
Gemcitabine is a deoxycytidine analogue structurally related to Ara-C. In many patients, it causes systemic symptoms of low-grade fever, fatigue malaise, myalgia, and arthralgia with paraesthesia. In about 10%, sensory neuropathy with paraesthesia can develop. A autonomic involvement has also been observed.

Muscle symptoms can appear as myalgias or as "radiation recall syndrome" in pre-radiated muscle. MRT can show oedema of the affected muscle and CK can be elevated.

Gemcitabine is often used in combination with taxanes, platinum compounds, or vinca alkaloids, all of which cause CINP, but does not seem to increase the risk of CIPN [70].

5-Fluorouracil
5-Fluorouracil (5-FU) is a pyrimidine antagonist. It is used as a single agent or in combination regimens for the treatment of many tumours, especially in the gastrointestinal system. A small number of cases of CIPN have been reported after treatment with 5-FU (accompanied by radiation and levamisol) [71] and after 5-FU chemotherapy in combination with folinic acid and eniluracil [72].

The hand-foot syndrome appears in particular when treatment consisting of 5-FU and capecitabine is applied.

Capcitabine
Capcitabine is metabolized to 5-FU. Except for observations from single cases [72], CIPN are unlikely. Cranial nerve lesions seem to appear rarely [73, 74].

The "hand-foot syndrome", or "palmar plantar erythrodysaesthesia" (PPE), has been observed in up to 10% of patients treated with capecitabine, but it is not specific and also appears in other drugs. Administration of the drug is followed within days by palmar and plantar paraesthesias and itching followed by the development of an erythematous and occasionally bullous palmar and plantar rash. It is thought to be due to a local skin reaction, but a relationship to neuropathy or damaged small skin nerves is postulated [75].

Mitotic Spindle Inhibitors
Vinca Alkaloids
Vinca alkaloids are mitotic spindle inhibitors, such as taxanes and podophyllin analogues (etoposide and tenoposide). The drugs interfere with microtubule assembly and mitotic spindle formation. They also influence axonal transport [76], structure, and function at many points. As with most toxic neuropathies, longer axons are more susceptible. Vinca alkaloids do not enter the blood-brain-barrier [77], which limits their use in neurological CNS disease.

Vinblastine, vincristine, and their semi-synthetic derivatives, vindesine and vinorelbine, are predominantly used for the treatment of haematológica and lymphatic malignancies and several other conditions. All are given by intravenous infusion. Vinca alkaloids produce a dose-related sensorimotor neuropathy. Vincristine and vindesine cause the most severe neurotoxicity, while vinblastine and vinorelbine are less toxic. A combination of vinorelbine with taxanes can be severe in patients previously treated with paclitaxel and has been observed in the course of a study monitoring [78].

Clinical Features
CIPN present usually within the first 3 months of treatment. Early symptoms are paraesthesias and pain in the hands and feet as well as distally accentuated hyperaesthesia. Weakness may also occur, in particular in wrist extensors and dorsiflexors of the toes [79]. Tendon reflexes are lost early on. Muscle cramps in distal muscles (eg, feet) are frequent, often persisting long after treatment cessation. Contrary to most other CIPN, mononeuropathies (femoral, peritoneal nerves), cranial nerve lesions (with diplopia, vocal cord paralysis [80], facial nerve palsy, and sensoneural hearing loss) have been described [81, 82]. A autonomic changes can result in gastrointestinal symptoms, such as paralytic ileus or megacolon [83]. Also bladder atony, impotence, orthostatic hypotension, and cardiac problems have been reported.

Rarely, severe neuropathy with quadriparesis occurs [84]. Inherited neuropathies [85, 86] may aggravate the expression of neuropathies and need to be considered before starting chemotherapy.

Laboratory Studies
Nerve conduction studies show axonal neuropathies with a reduced amplitude of motor and sensory action potentials with mildly reduced conduction velocities.

Prognosis and Treatment
There are no pharmacologic treatments to reduce or prevent CIPN induced by vinca alkaloids. A pharmacological approach with lacosamide has been proposed to reduce pain and allo-
Chemotherapy and Polyneuropathies

dynia in animal models [87]. Reducing dose levels and frequency of application may ameliorate the development of neuropathies. After cessation of therapy, coasting has also been described [22]. In severe cases, improvement occurs over months to several years and may be incomplete. A decreased risk of neuropathy and a more rapid recovery may exist in African Americans with at least one CYP3A5*1 allele [88].

Physical therapy and orthoses minimize the effects of motor deficits. Skin protection and management of neuropathic pain help patients with sensory deficits.

Inadvertent intrathecal injection of any of the vinca alkaloids results in severe ascending myeloencephalopathy that is usually fatal [89, 90].

Taxanes

Both drugs, paclitaxel and docetaxel, are widely used alone or in combination for the treatment of breast, ovarian, lung, and many other forms of cancer. Paclitaxel may produce more neuropathies than docetaxel [91]. Taxanes are frequently used in combination with other agents that cause CIPN. It is unclear whether additive or synergistic neuropathy results from this combination. There are two important issues concerning the transport vehicle of the drug: the transport mechanism is cremaphor [92], a non-ionic surfactant and a polysaturated castor oil which has side effects of its own, in particular allergic reactions; the other transport vehicle is abraxane, a protein-bound paclitaxel, which avoids the side effects of cremophor but unfortunately causes CIPN in this preparation. Other preparations of paclitaxel are taxoprexin, a DHA paclitaxel (omega-3 fatty acid), and xyotax, a PGA paclitaxel (poly-L-glutamic acid).

Taxanes hyperstabilize microtubule subunit cross-linking. This has the effect of increased stability of microtubules and decreased ability of the cell to dynamically reorganize the cytoskeleton. Also the formation of crystalline arrays of microtubule subunits in the cell or axon [93] occurs, which disrupts the axonal transport, the retrograde transport of target-derived trophic factors, and other vesicular components. Both processes interfere with axonal transport and result in neuropathy. In addition to microtubule changes, the ubiquitin-proteasome system (UPS) in axons with local activation of calpain/caspase cells and apoptosis may also be activated. Their mode of action is similar to epithelones.

Clinical Features

Sensory symptoms are common and dose-related [94]. Both drugs induce paraesthesias, loss of sensation, and dysesthetic pain in the feet and hands. Activities of daily life, fine motor tasks, such as buttoning and writing, can be impaired. Gait unsteadiness can be a result of sensory ataxia.

At examination, the vibratory threshold increases and perceptions of light, touch, and pin decrease in the feet more than in the hands. Deep tendon reflexes at the ankle may be lost but more proximal reflexes may be preserved.

Weakness is absent or mild, although motor neuropathies have been observed [95]. Lhermitte’s phenomenon may appear. A utonomic symptoms have been described, gastrointestinal symptoms and cardiac arrhythmia may occur.

An acute toxicity, caused by mitochondrial damage and small-fibre type lesions with up-regulation of PGP9.5 in the Langerhans cells, has been described and can be attributed to acute CIPN toxicity [96]. As the lesions are restricted to the afferent axon’s terminal arbor, it was suggested to name them “terminal arbor degeneration” [97].

Treatment with taxanes can also cause a proximal weakness syndrome independently of sensory symptoms. Myalgia/arthralgia syndromes are more frequent in paclitaxel and related to drug treatment, beginning 2–3 days after administration and lasting several days.

Laboratory Studies

Electrophysiological testing typically demonstrates that sural nerve potentials are reduced or absent in symptomatic patients with signs of axonal neuropathy.

Concurrent cis-platinum or alcohol abuse increases the risk of CIPN. ABCB1-allelic variation negatively influences the effect of docetaxel treatment [98] and the onset of neuropathy can be delayed which will be possibly a predictive factor for the development of CIPN.

Prognosis and Treatment

The sensory symptoms can be troublesome and typically remit within several weeks after treatment has been completed. Lowering the dose and lengthening the treatment may reduce difficulties in more symptomatic patients. However, long-term follow-up examinations describe a prolonged effect of CIPN in individuals with a negative effect on the quality of life [99, 100].

Other Microtubule-Stabilizing Agents

Epithelones

Epithelones are a group of microtubule-stabilizing agents, including epothilone A, epothilone B [101], and epothilone D. Distal sensory and motor neuropathy, similar to taxanes, have been reported from phase-III clinical trials [102, 103]. Also a specific effect on vibration perception has been described.

Eribulin

Eribulin (eribulin mesylate) is a non-taxane microtubule dynamics inhibitor with tubulin-based antimitotic activity. It is used in the treatment of patients with locally advanced or metastatic breast cancer who have previously been treated with other chemotherapies. Peripheral neuropathy (incidence 5%) was the most common adverse event resulting in the discontinuation of eribulin treatment. In animal experiments, eribulin seems less toxic compared to other drugs [104].

Podophyllin

Podophyllin is an alkaloid extracted from the May Apple or American mandrake and is considered both a spindle inhibitor as well as a topoisomerase inhibitor.

Etoposide (VP 16) and teniposide (VM 26) are chemotherapeutic agents derived from podophyllin. They disrupt mitotic
spindle formation and inhibit topoisomerase II as well. The drugs are extensively used in many different forms of cancer, often in combination with drugs that cause CINP. Although peripheral toxicity is generally accepted, usually by observations and case descriptions [105], data from large studies are missing.

Topoisomerase Inhibitors
Topoisomerase is an enzyme which interferes with repair of DNA damage and facilitates apoptosis. Topoisomerase II cuts and unwinds DNA. Type-I topoisomerase inhibitors are camptothecins (irinotecan and topotecan), and type-II inhibitors are ansacrine, etoposide, etoposide phosphate, and teniposide; they are used in several chemotherapies. For topotecan and teniposide, neuropathies of minor extent have been reported [106, 107].

Proteasome Inhibitors
Bortezomib is a polycyclic derivative of boronic acid that inhibits the mammalian 26S proteasome. The 26S proteasome is a large complex that is part of the ubiquitin degradation pathway. It regulates the homoeostatic level of many intracellular proteins including those involved in cell-cycle regulation and apoptosis. The proteasome degrades the intracellular inhibitor of NFκB (IκB). Bortezomib increases the level of the inhibitor and decreases the activity of NFκB. This down-regulates the expression of proteins that promote cell division and proliferation and enhances apoptosis. Also, secretion of cytokines in the bone marrow is suppressed. It also enhances oxidative stress by up-regulation of p53, p21, p27, p38, MAPK, and JNK. Genetic factors may be implicated in the susceptibility [108].

Carfilzomib is an irreversible proteasome inhibitor with less neurotoxic side effects [109, 110].

Clinical Features
The neuropathy is dose-related and cumulative. It is predominantly sensory, distally accentuated, and depends on the duration of treatment. It often causes neuropathic pain probably due to small-fibre involvement. Patients experience sensory loss (numbness) and, due to small-fibre loss, pain which is perceived as burning, sharp, cold, or electric. This painful association is particularly worrying [111, 112].

Also autonomic changes with postural hypotension have been reported. Increased age is an additional risk factor. In trials, CIPN occurred in 37–44 % of patients with multiple myeloma [113]. Usually, it is a reversible duration-of-treatment-dependent neuropathy [114–116].

In a few cases, demyelinating neuropathies [117], which are probably dysimmune [118], have been observed as well.

Laboratory
Electrophysiological changes demonstrate axonal loss as the drug has become more widely used, more prevalent, and more severe cases of neuropathy have been reported [119]. Pretreatment with thalidomide is a serious risk factor for the development of CIPN.

A demyelinating neuropathy has also been observed [118], even in combination with thalidomide [119].

Others
Arsenic Trioxide
Arsenic trioxide has recently been introduced for the treatment of refractory forms of cancer [120]. It is an inorganic arsenic compound that has been known for many years to cause severe and sometimes fatal peripheral neuropathy. A recent single-agent trial, however, described few neurotoxic effects [121].

Thalidomide and Lenalodimide
Thalidomide has a sad record of teratogenic effects due to its use in pregnant patients in the 1950s and 1960s. Since then it has been used in erythema nodosum leprosum, and as a potent VEGF inhibitor in multiple myeloma, Waldenstrom’s macroglobulinaemia, myelodysplastic syndromes, acute myeloid leukaemia, myelofibrosis, graft versus host disease, prostate cancer, renal cell cancer, malignant brain tumours, Kaposi sarcoma, and cancer.

The type of neuropathy is predominantly sensory, with numbness and pain in hands and feet. All sensory qualities are affected, reflexes may be preserved. Cramps of small foot muscles occur. Neuropathies develop in 20–40 % of patients [122, 123]. Frequency of neuropathy increases with age and cumulative doses or duration of treatment; vulnerability in aged persons is also a major concern [124].

Lenalidomide is an analogue (alpha-3-aminophthalimidoglutaminimide) and less neurotoxic in the PNS [125–127].

Suramin
Suramin (polysulfonated naphthylurea) has been used for the treatment of tropical parasitic diseases. It can cause nephropathy and, when used in cancer patients, 2 types of CIPN: a mild distal axonal neuropathy and an acute form resembling acute polyradiculitis [128].

Biologicals
In addition to the “classical drugs” causing CIPN, some biologicals are also mentioned, usually when administered in combination with neurotoxic drugs, which makes it difficult to assess the true effect and incidence. Three antibodies have been mentioned to cause CIPN, and except for brentuximab, where sensory neuropathies have been described, bevacizumab and trastuzumab have been considered as well. An interesting approach to this question is made by http://www.ehealthme.com [129], where a total of side effects is listed for a defined period of time.

Antibodies
Bevacizumab
Neuropathy as a side effect of bevacizumab has not made it to the “top ten” of its most frequent side effects [129]. As of August 2011, 13,485 persons reported side effects; 16 individuals (0.12 %) had a sensory neuropathy, which occurred in the first month, which makes a cumulative effect unlikely. Other concomitant drugs were also used, which makes it difficult to evaluate. A possible association with paclitaxel has been observed. Presently, no clear evidence exists.
Brentuximab Vedotin (SGN-35)

Brentuximab vedotin is an anti-CD30 monoclonal antibody in combination with monomethyl auristatin E (an antitubulin agent). It is used in the treatment of Hodgkin’s lymphoma. Sensory neuropathies have been described [130]. A general opinion cannot be expressed presently.

Trastuzumab

Trastuzumab was analyzed on http://www.ehealthme.com [129] with regard to reported side effects. As of August 2011, 64,443 persons reported side effects, among them 8 individuals (0.012 %) reported a sensory neuropathy. Contrary to bevacizumab, the neuropathy was most often observed after one year (50 %) and 2 years (25 %), which makes a cumulative effect likely. Associated drugs were cyclophosphamide, gabapentine, and femara, but also other drugs, which makes the interpretation difficult. In combination with conventional chemotherapies, neuropathies have been described [131].

Interferons

Interferon-α

Interferon-α is used in the treatment of leukaemia and lymphoma as well as of hepatitis C. It can cause a distal symmetric sensory neuropathy, which can also cause pain and paraesthesia, mild loss of pain and temperature perception [132]. The NCV shows axonal loss.

Hormones

Hormonal treatment has been assessed in comparison with chemotherapy in breast cancer. A trial of primary endocrine therapy using aromatase inhibitors (anastrozole and exemestane) in patients with ER-positive and/or PgR-positive breast cancer showed grade-2 neuropathies occurring in 30 % of patients receiving chemotherapy, while hormonal treatment was well-tolerated [133]. Focal neuropathies, such as the carpal tunnel syndrome, may increasingly occur during aromatase therapy [134].

Radioisosensitizers

Misonidazole

Misonidazole has been used as an adjunct to radiation therapy as a radiosensitizer. It causes a sensory, often painful neuropathy and is dose-related (cumulative dose > 16–18 g) [135]. The incidence can be up to 30 % if the cumulative dose has been reached [135]. The newly used radiosensitizer motexafin gadolinium has not yet been reported to cause neuropathies.

Vitamins

Vitamin A and retinoid treatment are used in haematological diseases. Not only muscle cramps and myalgia but also sensory symptoms have been reported. The mechanisms are not fully understood.

Conversely, in animal experiments, a protective effect of retinoids in CIPN has been proposed [136].

Tipifarnib

Tipifarnib is an oral non-peptidomimetic farnesyl transferase inhibitor used in both solid tumours and haematological malignancies such as acute myeloid leukaemia [137]. Toxicity is predominantly haematological, mild neuropathies have been reported [138].

Cancer Type and Neuropathy: Myeloma

Two types of malignancy – lung cancer (SCLC) and myeloma – have several types of disease-associated neuropathies. In lung cancer, it is a paraneoplastic, subacute sensory neuropathy (SSN), which usually appears at the onset of malignancy prior to chemotherapy. Neuropathies in multiple myeloma can appear at any time, due to several aetiologies, and have been subject to reviews [139]. This is of importance as the current drug treatment has a high potential for the development of neuropathies, and also because it is generally assumed that a pre-existing neuropathy may increase the risk for a CIPN. Possible factors from myeloma and also genetic factors may be responsible for the expression of a neuropathy [140, 141].

A neuropathy caused by therapy can be dose-limiting in up to 10 % [142]. Although no specific treatment is available, dose modification needs to be considered in case of paraesthesias and pain. Treatment should be modified or reduced until toxicity resolves. Treatment also consists of symptomatic management of neuropathic pain, protection against sensory loss, and physical therapy. Elderly patients may be less able to withstand the side effects associated with newer treatment regimens [143].

The rarely observed POEMS syndrome is associated with several types of neuropathies. Treatment results have been summarized in a Cochrane review [144].

Differential Diagnosis

The differential diagnosis of CIPN is mainly based on the vital question of what chemotherapy the patient has received so far and if neurotoxicity can be expected from the substance and its dose. Several drugs applied for chemotherapy do not cause CIPN, which can be an important factor in discussing a patient’s symptoms and signs at evaluation.

Differential diagnosis often considers paraneoplastic neuropathies, which tend to appear early in the course of the disease and often contribute to the detection of cancer.

A cute types of neuropathies, such as the Guillain-Barré syndrome and CIDP, have been observed to appear in lymphoma and Hodgkin’s disease patients [145] and are related to the tumour type. Demyelinating neuropathies have been described in suramin treatment, and also in rare cases of bortezombin administration [117].

Meningeal carcinomatosis rarely presents as a neuropathy mimic, either as cauda equina presentation or rarely as an ascending polyradicular form. Clinically, often the association with CNS symptoms is helpful. Cauda equina lesions involve the sphincteric function as well, which is not the case in CIPN. As a rule, early pain appears.

Neurolymphomatosis [146] is a rare type of lymphomatous spread in lymphoma. It can occur either isolated in the periph-
eral nerves or in a combination of peripheral nerves and CSF, which is a matter of definition. The presenting signs can vary from a symmetric CIDP type to a multiplex type and solitary peripheral nerve involvement. The diagnosis is difficult but imaging may help; finally, a biopsy is necessary. Also intravascular lymphoma can affect peripheral nerves [147].

Neuroleukaemiosis

This is a recently coined term [148] describing often symmetric and diffuse involvement of peripheral nerves. It has also been noted to appear as a multifocal neuropathy in M4/M5 leukaemia.

Historically, it appears that autopsy series in the pre-chemotherapy era, were well aware of this phenomenon.

Cauda Equina Syndrome

Malignant compression of the cauda equina may be caused by a tumour, vertebral collapse, lipomatosis following steroid treatment, or chemical injury by intrathecal therapy and has been reported as a side effect of cytosine arabinoside long-term application [68]. Usually, additional signs such as a sphincter’s involvement or back pain make the diagnosis likely. Intramedullary metastases are extremely rare but they can also mimic a sensorimotor neuropathy.

Prevention

Preventive drugs can potentially counteract cancer therapy. This has been the problem with several previously used preventive therapies. Several drugs have been used, such as vitamins (B and E) [149], glutation, alpha lipicoic acid, acetylcysteine [150, 151], amifostine, calcium, magnesium, diethylthiocarbamate [152], dithiocarbamate, Org 2766, oxcarbazepine [153], or erythropoetin [154–157]. For platin drugs, a Cochrane review states that chemoprotective agents do not seem to prevent CIPN [158].

Symptomatic Treatment

Despite the failure of drugs to prevent CIPN, several symptomatic treatments are available and should be considered in each individual case.

Oxaliplatin’s Acute Toxicity

The treatment and prevention of acute oxaliplatin toxicity have been an issue. Two basic avenues exist: (1) Ca and Mg administration or (2) carbamazepine or oxcarbazepine, which impacts the affected channels.

Neuropathic Pain and Dysaesthesia

Pain and paraesthesia can be a severe effect of some chemotherapy regimens, in particular taxanes and bortezomib. The use of drugs directed against neuropathic pain with anticonvulsants, antidepressants, in severe cases opioids, and, recently, also topical local anaesthetics has to be decided on according to the symptoms of each patient.

Prevention

The question of whether the administration of anticonvulsants can prevent neuropathies is increasingly discussed. Considering the concept of action of anticonvulsants this may not be likely; considering the effect that less grade-3 toxicities appear during treatment, this effect of subjective improvement can in a way be regarded as prevention of higher toxicity.

Physical and Occupational Therapies

CIPN, apart from sensory symptoms and pain, often have a loss of proprioception, which is a highly incomming effect in A D L S and gait. These effects are often underestimated. It is likely that the amplified application of physical and occupational therapies, which activate other senses (vision, hearing) as well, can compensate sensory deficits and might improve them through systematic training [159].

Rehabilitation and Cancer Rehabilitation

Rehabilitation for cancer patients is increasingly offered [160]. This is a tremendous success since, in the past, cancer in a patient often banned further rehabilitation. Without dwelling on the different types of cancer rehabilitation, neuropathies and sequelae of CIPN deserve particular attention [159]. Further, it is obvious from several studies (on taxanes) that often CIPN are not completely reversible and leave the patient distinctly disabled [161].

Summary

CIPN caused by cancer treatment is gaining importance, as several effective therapies damage the peripheral nerves by various mechanisms. Despite different mechanisms of drugs, it is hoped that common mechanisms in the structure or function of peripheral nerves may help to develop preventive strategies.

For the clinician, the knowledge of drugs given to the individual patient and the cumulative doses are important. Increasingly, also other substances, in particular biological substances, may play a role by influencing the metabolism.

Symptomatic treatment with regard to sensory and/or motor symptoms and pain needs to be considered as well as concepts of rehabilitation to improve a patient’s functions and quality of life.

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The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-PERINOMS) Study: An Answer to the Unsettled Question of Drug-Related Neuropathy Assessment in Cancer Patients

Guido Cavaletti on behalf of the CI-PERINOMS Study Group*

Abstract: Chemotherapy-induced peripheral neuropathy is a potentially severe and dose-limiting side effect of anticancer treatment. Despite its clinical relevance several crucial aspects of chemotherapy-induced peripheral neuropathy remain unsolved. Among them, the proper assessment of the occurrence and severity of this side effect is one of the most important.

Chemotherapy-induced peripheral neuropathy severity is generally assessed using common toxicity criteria scales, but most of them mix objective and subjective impairment and disability aspects. In addition, marked inter-observer disagreement exists using these scales, leading to misinterpretation of the results. Various other scale types exist (eg, composite scales based on clinical and instrumental examinations; patient-reported outcome measures based on self-administered questionnaires), but these outcome measures have never been subjected to formal clinimetric evaluation.

The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-PERINOMS) study is a collaborative effort of 20 European and US oncology and neurology centres specifically designed to compare the validity and reliability of different methods proposed for the assessment of chemotherapy-induced peripheral neuropathy in a formal way. The final aim of CI-PERINOMS is to propose a standardized well-evaluated set of measures for optimal assessment of chemotherapy-induced peripheral neuropathy in future clinical studies. Eur Assoc of NeuroOncol Mag 2012; 2 (1): 37–40.

Key words: chemotherapy, neuropathy, assessment, Rasch analysis, toxicity

Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a frequent and sometimes severe side effect of several very effective anti-cancer drugs [1, 2]. In fact, sensory impairment is potentially dose-limiting in patients treated with platinum drugs (cisplatin, oxaliplatin, less frequently carboplatin), thalidomide, or bortezomib, while sensorimotor CIPN is typical when anti-tubulin drugs (taxanes, epothilones, and vinca alkaloids) are administered [3]. Moreover, when several neurotoxic anti-neoplastic drugs are used together in chemotherapy regimens, the incidence and severity of CIPN changes due to the appearance of combined neurotoxicity.

Incidence

The incidence of CIPN has never been clearly established, largely due to methodological issues in its assessment [4–7]. Outcome measures differ from one study to the other, and interobserver disagreement has been described in the use of various well-known neurotoxicity rating scales [7], making it difficult to interpret literature data properly in terms of incidence and severity of CIPN. Moreover, several neurotoxic anti-neoplastic drugs are used together in chemotherapy sche-

dules for the treatment of selected kinds of solid or haematological cancers, with a subsequent possible increase in the incidence and severity of CIPN and/or the appearance of combined neurotoxicity.

Toxicity

Although some aspects of CIPN are similar among the various drugs, every class of drugs has its characteristic toxicity profile [3]. Typically, platinum compounds produce a pattern of sensory loss consistent with primary ganglionopathy and proprioceptive loss may result in ataxia leading to severe functional impairment [8, 9]. Besides its toxicity to the dorsal root ganglia and peripheral nerves, cisplatin is also toxic to the cochlea hairy cells leading to deafness [10]. A most pure sensory impairment in pain, thermal and touch perception are the most common clinical features experienced by multiple myeloma patients treated with bortezomib and/or thalidomide [11, 12]. All the various classes of anti-tubulins induce distal sensorimotor neuropathy, but reduced pain/thermal perception and touch hypoaesthesia with non-painful paraesthesias are always more severe than motor impairment [13, 14].

Patients often report neuropathic pain after the administration of platinum drugs, paclitaxel, or vincristine [15], but it is particularly severe in the case of bortezomib administration in the treatment of multiple myeloma [12, 16–18].

Autonomic impairment is infrequent and may result in a wide spectrum of symptoms, including orthostatic hypotension, constipation, sexual dysfunction, and micturition disorders. This can be clinically relevant particularly in vincristine-treated subjects [19].
CI-Perinoms

Since one of the main issues in the proper assessment of CIPN is represented by the absence of scientifically sound instruments (as depicted by Cavaletti et al [20]), we recently completed the Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-Perinoms) study, based on the collaboration among 20 US and European oncology and neurology centres (see list of centres and principal investigators at the end of this article) [21].

The 2 fundamental and original objectives of the CI-Perinoms study are (1) the analysis of the current status of CIPN assessment and (2) the implementation of a rigorous clinimetric approach [22], aiming to present a set of scientifically sound (valid and reliable) scales for the assessment of CIPN in future clinical studies.

It is now recognized that any useful scale to assess a medical disorder should be simple, valid, reliable, responsive, and it should provide results that can be easily interpreted. Although these concepts might appear quite obvious, some of them deserve to be considered in detail. This is the case for validity and reliability, 2 fundamental methodological aspects whose importance is frequently underestimated. None of the most widely used scales to assess CIPN properly fulfill these requirements [23].

Validity
Various types of validity are described.
- Face validity refers to the apparent sensibility of the measure and its components. It indicates whether the scale appears to be assessing the desired qualities and represents the subjective judgement based on a review of the measure itself by one or more experts.
- Content validity consists of a judgement by experts evaluating whether an outcome measure captures all the relevant or important contents or domains of an illness.
- Construct validity is demonstrated by examining the relations between a newly created test and other tests to show that the new test measures the same “construct”. Evidence for construct validity is gathered by undertaking a series of studies to determine
  - convergent validity (the extent to which a measure correlates with other measures of related entities),
  - discriminant validity (the extent to which a measure does not correlate with measures of different entities), and
  - divergent validity (the extent to which a measure correlates with measures of opposite entities).
- Criterion-related validity is demonstrated by examining the accuracy of a test compared with a “gold standard”.

Reliability
Regarding reliability, a reliable measure is one that produces results that are accurate, consistent, stable over time, and reproducible. There are 3 different types of reliability.
- Internal consistency is the extent to which items comprising a scale measure the same concept.
- Observer reliability is the agreement between observers or within an individual observer.
- Test-retest reliability is the agreement between observations made by the same rater on 2 different occasions.

The main aim of CI-Perinoms is to propose a standardized well-evaluated set of measures for optimal assessment of CIPN in future clinical studies starting from a series of instruments which have been used in daily practice and clinical trials in CIPN patients (Table 1).

In CI-Perinoms, the clinimetric assessment of CIPN was performed at 2 different levels of investigation: (1) the core study required the evaluation of patients to be done with common devices. As such, an evaluation can be performed at any medical site. (2) The extended study included the use of additional methods of assessment, including specific devices (ie, graduated tuning fork, 10 g monofilament) and nerve conduction studies in order to ascertain whether this approach could give a more careful and clinically relevant estimate of CIPN. Patients were also asked to complete a questionnaire to obtain a set of questions useful to develop a CIPN-specific Overall Disability scale specific to CIPN and based on the Rasch analysis (RODS-CIPN) [34, 35].

To assess inter- and intra-observer agreement 2 investigators in each participating centre applied the selected impairment and activity limitation scales. Subjects were examined twice within a period of 3 weeks (visits 1 and 2) and the patient-reported outcome measures presented in Table 1 were completed at both visits by each patient to allow a test-retest evaluation. A focused electrophysiological study was performed only once at visit 1.

Since the National Cancer Institute Common Toxicity Criteria version 3 (NCI-CTC v.3) for neuropathy is still the most

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NCS: nerve conduction studies; TNSc: Total Neuropathy Score, clinical version [24–27]; mISS: modified INCAT sensory sum score [28]; C-ODSS: calibrated-overall disability sum score [29]; PI-NRS: 11-point pain intensity numerical rating scale [30]; QLQ-CIPN20: EORTC 20 items CIPN specific quality-of-life questionnaire [31]; QLQ-C30: EORTC 30-item questionnaire for quality of life in cancer patients [32]; QoL-PS: quality of life personal score; VAS: visual analogue pain scale [33].
widely used method for assessing sensory neuropathy in most studies of CIPN, this instrument was considered the clinical standard for the study, to be compared with the selected methods for its effectiveness and appropriateness.

At the end of the enrolment period 281 patients were available for the analysis which is still ongoing.

We are convinced that CI-Perinoms, the first study ever performed to approach the CIPN assessment issue with a clinimetric method, will eventually provide the basis for an answer to a still unmet clinical need in the treatment of cancer patients. The final aim is to provide a standardized set of outcome measures for future clinical studies in CIPN.

Conflict of Interest

GC has no conflict of interest to declare.

The CI-PERINOMS Study Group

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Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization Study

References:


22. van Nes SI, Faber CG, Merkies IS. Outcome measures in immune-mediated neuropathies: the need to standardize their use and to understand the clinimetric essentials. J Peripher Nerv Syst 2008; 13: 136–47.


Recently, the EANO has launched a new fellowship programme specifically aiming at supporting the mobility of young brain tumour researchers within Europe. Motivated by the wish to gain research experience abroad and to increase my professional network in the field, I applied for such an EANO Fellowship Grant and am very proud to have been selected as the first awardee in early 2011. The EANO Fellowship Grant gave me the opportunity to carry out the project “BRAF V600E mutations in brain metastases of solid cancers” from April to September 2011 at the Department of Neuropathology, Ruprecht-Karls-University, Heidelberg, Germany (Chair: Dr Andreas von Deimling), a distinguished laboratory well-known for its groundbreaking work on brain tumour neuropathology and biology including the recent establishment of isocitrate dehydrogenase 1 (IDH1) R132H immunostaining for neuropathological work-up of gliomas.

In the funded project, we investigated expression of the mutated BRAF V600E protein in a large series of tumours from patients with brain metastases of solid cancers. Brain metastases are common (up to 10 times more common than gliomas), have a poor prognosis, and, surprisingly enough, are so far grossly underrepresented in the scientific literature [1]. Current treatment algorithms comprise mainly neurosurgery and radiotherapy, while systemic therapies have not shown much efficacy so far. There is a strong need to single out novel therapeutic targets and strategies for patients with brain metastases. Activating mutations of the serine threonine kinase v-RAF murine sarcoma viral oncogene homolog B1 (BRAF), most commonly of the V600E type, are found in a wide range of tumours, and specific inhibitors targeting BRAF V600E protein have been developed [2]. Based on the available data on BRAF mutations in primary tumours, we hypothesized that a proportion of brain metastases also harbours the mutation and therefore may be amenable to BRAF-inhibiting therapeutics. We analyzed BRAF V600E-mutant protein expression using a recently generated mutation-specific antibody [3] in a series of 1120 tumour specimens (885 brain metastases, 157 matched primary tumours, and 78 matched extracranial metastases) of 874 brain metastasis patients. The aim of our study was to define the target population for BRAF-inhibiting therapies among brain metastasis patients and to analyze the tumoural expression patterns of BRAF V600E protein. In 85 cases, we performed validation of immunohistochemical results by BRAF exon 15 gene sequencing. BRAF V600E protein was found in brain metastases of 55.3 % of melanoma cases, 6.7 % of ovarian cancer cases, 5.5 % of colorectal cancer cases, 0.3 % of lung cancer cases, 2/6 of thyroid cancer cases, and 1/2 chorioncarcinoma cases. BRAF V600E expression showed high intratumoural homogeneity and was consistent among different tumour manifestations of individual patients, thus providing a rationale for targeted BRAF inhibitor therapy in selected patients. VE1 immunohistochemistry and BRAF exon 15 sequencing were congruent in 97 % of cases. VE1 immunostaining was more sensitive than gene sequencing in our series, as it identified small BRAF V600E expressing tumour cell aggregates in 10/15 cases with inconclusive genetic results. In general, we found homogenous anti-BRAF V600E immunostaining intensity throughout well-preserved tumour tissue. In none of the cases, we saw focal BRAF V600E expression, providing evidence for a monoclonal origin of BRAF V600E mutated metastases. However, we detected variability of immunostaining intensity among different tumours. It remains to be clarified whether these differences relate to tissue preservation, qualitative differences of the immunostaining reaction, or whether they reflect true differences in BRAF V600E protein expression. It will be of interest to correlate immunostaining intensity to response to treatment with BRAF inhibitors within clinical trials and we have begun to design appropriate trials in cooperation with the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumour Group. Interestingly, in our series, melanoma patients with BRAF V600E mutant protein expressing tumours were significantly younger at diagnosis of the primary tumour and at operation of brain metastases than patients with non-mutated tumours. From our work, we concluded that expression of BRAF V600E mutant protein is found in approximately 6 % of brain metastases and that immunohistochemical visualization of V600E-mutant BRAF protein is a promising tool for patient stratification for BRAF-inhibiting therapies and may facilitate molecular tumour characterization in the clinical setting [4].

My research stay in Heidelberg was a very valuable and scientifically productive time. I could not only profit by increasing my knowledge and scientific experience through the work and interaction with my colleagues in Heidelberg, but am also happy to have made many new friends during my fellowship. Dr von Deimling and his colleagues made me feel very welcome at their institute and were very supportive throughout my entire stay. I am very grateful for this and for the opportunity the EANO Fellowship Grant provided me with and truly hope that the EANO continues this programme to support the careers of more young scientists interested in the fascinating field of neuro-oncology. I feel that we need strong collaborative efforts to make more progress and to fight brain cancer more efficiently. To my mind, interaction and mobility of European researchers is pivotal for the establishment of strong networks for powerful scientific co-operations. Therefore, I strongly encourage all brain tumour researchers interested in a research stay in another European laboratory to apply for an EANO Fellowship Grant and would be happy to share my experience with the organisation of such an exchange or the development of the grant application.
References:

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**Background**

In February 2008, I started a PhD programme at the VU University Medical Center aiming to explore the end-of-life (EOL) phase of high-grade glioma (HGG) patients. The EOL phase begins when the patient’s condition deteriorates and no further tumour treatment is possible. Since there is to date no cure for high-grade glioma patients, everyone of them will eventually reach this phase. There is only limited data on this EOL phase.

For this reason, we performed a retrospective chart study in the Netherlands aiming to detect problems and symptoms in the EOL phase [1]. Furthermore, we started a large, systematic, historical cohort study interviewing relatives and physicians of deceased HGG patients who were diagnosed in 2005 and 2006 in 3 Dutch hospitals (VUMC Amsterdam, MC Haaglanden The Hague, AMC Amsterdam). The aim of this study was to further explore the EOL phase of HGG patients with respect to symptoms, signs, quality of life, caregiver burden, quality of EOL care provided, and EOL decision-making.

Health care provisions in the EOL phase vary by country. Legislation and opinion regarding medical EOL decisions vary among countries and cultures. This underscores the importance of comparing these issues among various countries and cultures.

In 2008, Dr Wolfgang Grisold and Dr Stefan Oberndorfer from the Kaiser-Franz-Josef Hospital in Vienna published one of the first papers examining the end-of-life phase of HGG patients [2]. During the 2008 EANO conference in Barcelona, we discussed the extension of our project with 3 Austrian centres, Kaiser-Franz-Josef (KFJ) Hospital, Vienna (Drs Grisold and Oberndorfer), Vienna General Hospital (Dr Christine Marosi), and Medical University of Innsbruck (Dr Günter Stockhammer), as well as one Scottish centre (Edinburgh Center for Neuro-Oncology, Dr Robin Grant).

I applied for the EANO Educational Visit Grant to visit the 3 Austrian centres participating in our international study. My goal was to help start up the project abroad, get better acquainted with our foreign colleagues, and gain insight into the care in the EOL phase for Austrian patients. Furthermore, it would add to my personal development to observe the care for neuro-oncological patients and the practice of neurologists in a foreign country.

**Educational Visit**

In August and September 2010, I visited Austria for 3 weeks. I spent the first week of my visit in Innsbruck visiting the centre of Dr Stockhammer. Afterwards, I spent 2 weeks in Vienna, visiting 2 different neuro-oncology groups: the group of Drs Grisold and Oberndorfer, neurologists at the KFJ hospital, and the group of Dr M arosi, oncologist at the Vienna General Hospital.

**The International Project**

In Innsbruck, I met the project participants, Dr Stockhammer, Dr Schauer-Mauer, Dr Holzner, and Dr Giesinger, to discuss the protocol and practical aspects of carrying out the study. During my visit, our study protocol was presented to the ethics committee and accepted conditionally. Drs Holzner and Giesinger, medical psychologists highly active in quality-of-life research, showed me some of the projects they are working on which added to my knowledge on this research topic.

A central Viennese ethics committee had already approved our study protocol and both centres started inclusion of relatives. At the KFJ hospital, the first questionnaires to relatives had recently been sent out. Response was relatively low and it proved difficult to track relatives. We discussed how best to enhance the response rate. At the Vienna General Hospital, a PhD student (Dr Birgit Flechl) worked on the study and the inclusion process went quite well. It was helpful to share experiences and discuss (future) data analysis.

**Neuro-Oncological Care in Austria**

At the 3 different neuro-oncological centres, I attended ward rounds, neuro-oncological outpatient clinics, and multidisciplinary neuro-oncological tumour board meetings. Furthermore, I joined a radiotherapist for a day at the KFJ hospital. It was interesting to compare the various tumour board discussions with our own tumour board at the VU University Medical Center. Although the initial approach varies between hospitals, the decisions taken are quite similar. The same holds true for treatment of brain tumour patients at the various outpatient departments.

**Social Events**

There was also time for social events: with Dr M arosi I visited the “Kunsthistorische Museen” and afterwards we had a traditional Austrian dinner. On the last night of my visit in Innsbruck, I was invited for the yearly barbecue with the neuro- oncology group on a mountain close to Innsbruck. A great night of Austrian hospitality!

**Progress of the Study**

In the meanwhile, the identification and inclusion of relatives and physicians of Austrian patients progressed well. By December 1, 2011, the inclusion of relatives and physicians from patients treated at the Medical University of Innsbruck was...
completed (Figure 1). The 2 Viennese centres completed the inclusion of relatives (Figure 2), the inclusion of physicians in Vienna is still ongoing.

Furthermore, we are obtaining data from relatives and physicians of patients treated at the Edinburgh Centre for Neuro-oncology, Edinburgh, Scotland. Comparative data analysis is planned for the second half of 2012.

**Conclusion**

My visit to Austria was a great opportunity to get better acquainted with the colleagues involved in our international project. I was able to help start up the project, share experiences, and discuss future directions. Data collection advanced in the year after my visit.

I saw different aspects of neuro-oncological care in various Austrian hospitals, which added greatly to my personal and professional development. The health care system in Austria varies from the Dutch system, and even in between the Austrian centres I noticed differences in approaches. However, there are many similarities as well and I think in the end, patients are treated more or less the same in both countries.

### Acknowledgements

Thanks to Dr Grisold, Dr Marosi, Dr Oberndorfer, and Dr Stockhammer for the invitation and hospitality. Special thanks to J Egeter, B Flechl, and C Sax for their extensive efforts in approaching physicians and relatives. Finally, thanks to Dr M Taphoorn for his feedback on this report.

### References:


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Case Report: A 52-Year-Old HIV-Seropositive Patient with Hodgkin’s Disease

Khê Hoang-Xuan1, Karima Mokhtari2, Laurent Capelle3

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Case Report

A 52-year-old man presenting in June 1997 with Hodgkin’s disease (grade II) was treated with an MOPP chemotherapy regimen (methylchlorethamine, vincristine, procarbazine, prednisone) followed by mediastinal radiotherapy with a total dose of 40 Gy at 1.8 Gy per fraction.

Ten years later, in 2007, he described a 2-year history of paraesthesias in the feet bilaterally. Numbness and tingling gradually progressed, ascending upward to include the legs, with a disturbance of pain and temperature sensation across his upper abdomen and lower chest. In the weeks preceding his admission, he had developed weakness in his lower and upper extremities as well as bladder sphincter dysfunction.

An MRI was performed showing an enlargement of the cervical and upper thoracic spinal cord with a hyperintense signal in a T2-weighted image from C3 to T7 (Figure 1), with an intramedullary contrast-enhancing lesion on C6.

What’s Your Diagnosis?

A spinal biopsy was performed and the pathological diagnosis was a glioblastoma (WHO grade-IV astrocytoma). Because this spinal tumour occurred in the field of a previous radiotherapy performed 10 years earlier, this glioblastoma might be a radiation-induced tumour, as previously described in Hodgkin’s disease [1]. The main differential diagnosis would be radiation-related myelitis (radionecrosis) but this diagnosis was excluded by the biopsy. Doses below 45–50 Gy in 1.8–2-Gy fractions are considered safe and are rarely associated with injury to the spinal cord. However, several case reports of radiation myelitis have been observed with such doses when given in conjunction with high-dose chemotherapy.

Reference:


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Figure 1. Enlargement of the cervical and upper thoracic spinal cord with a hyperintense signal in a T2-weighted image from C3 to T7, with an intramedullary contrast-enhancing lesion on C6.
Case Presentation

A 38-year-old female was admitted with suddenly appearing prickling in both hands. The neurological examination demonstrated no abnormalities. An MRI study of the head showed a mass lesion within the upper and middle cerebellar peduncles on the right side, measuring about 3 cm in diameter. The lesion bulged into the fourth ventricle and led to its partial occlusion. It appeared hypointense on T1-weighted images and exhibited a 1-cm slightly contrast-enhancing tumour part (Figures 1–3). Surgery was performed via median suboccipital craniotomy through the fourth ventricle using intraoperative electrophysiological monitoring of the lower cranial nerves. The tumour was significantly firmer than CNS substance and was removed gross-totally from the cerebellar peduncles by means of microsurgical technique. The postoperative course was uneventful besides transitory right-sided dysdiadochokinesia, intermittent dizziness, and vertigo.

Case Resolution: Rosette-Forming Glioneuronal Tumour of the Fourth Ventricle (RGNT)

Histological examination of the tumour revealed a rosette-forming glioneuronal tumour of the fourth ventricle (RGNT), a benign (WHO grade I) tumour of young adults, arising in the fourth ventricular region (Figures 4, 5). This rare tumour entity first described by Komori et al in 2002 [1] was included in the WHO classification of tumours of the central nervous system.
In 2007, histologically, it consists of 2 distinct components, one with uniform neurocytes forming rosettes and/or perivascular pseudorosettes, the other being astrocytic in nature and resembling pilocytic astrocytoma. More than 40 cases have been analysed and described since then. Mean age of patients was found to be about 30 years with a female-to-male ratio of 2:1 [2]. Despite the benign histology and postoperative long-term stability of the patients without additional therapy, long-term follow-up is advisable in the face of limited experience and seldomly reported recurrences.

Figure 4. H&E-stained histological slide, showing perivascular pseudorosettes within the tumour.

Figure 5. Synaptophysin immunoreactivity in the pericapillar space, confirming neuronal differentiation.

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In Europe, nurses who provide care for cancer patients are found in a clinical or a palliative-care setting, like a hospice, a nursing home, or in home care. To provide quality care for patients with cancer, education and evidence-based oncology nursing are of importance and should be accessible in every European country, through nursing schools, journals, associations, congresses, and through the internet (e-learning). Education is aimed at several competences that oncology nurses need regarding patient care: assessment of health status, diagnostic aspects of nursing care, and, as a result of that implementation and evaluation of interventions, planning and coordinating care, and finally maintenance of a professional level and competence.

## Cancer Nursing

Regarding cancer nursing practice, there appears to be a great variety of competences, education, working conditions, and professional status between and even within European countries [1]. A survey performed by the European Oncology Nursing Society (EONS) among its national member societies revealed that oncology nursing programmes are found in 16 of the 20 participating countries, with the duration of these programs ranging from 6–24 months (40–800 hours), and that these oncology nursing training programmes make use of the core programmes of EONS in various ways. It became clear that there is a high demand for oncology nurses in many European countries. Oncology nursing is recognized as a specialized area in 11 countries and all these countries except 3 have specialized/expertise roles for nurses in palliative care. The survey also showed that specialized roles for cancer protection and prevention are gradually increasing. Senior positions for practicing nursing at the masters’ degree level exist in 4 countries, nursing practices development units/departments are common in only a few countries, including England and Sweden [2].

## Knowledge and Skills

Because patient advocacy, provision of support, and information about disease and its treatment for patients and caregivers are important aspects of the coordinating role of the oncology nurse, it is recommended that nurses should become skilled communicators within the multidisciplinary team. As a consequence, in many European countries the role of the oncology nurse has developed to the extent that in many centres (neuro-) oncology nurses take a leading role in the care of oncology patients. Specialization in oncology nursing is aimed at providing support for a specific group of cancer patients and their families and to further develop care. So, the specialized oncology nurse requires specialized knowledge and skills [3].

## Exchange of Knowledge

Admitting that neuro-oncology nursing is a specialty in oncology care and cure has been the starting point of the motivation for the contents of the nursing research and care programme at the next EANO conference. What could be the topics that address the demand of education for more or less trained neuro-oncology nurses? What themes could be worthwhile to be discussed that will add important skills and competences to the understanding of oncology nurses and other healthcare personnel that result in optimal neuro-oncology care?

A colleague from Timone Hospital in Marseille, who started as a neuro-oncology nurse in September 2011, came to visit me in the Netherlands for 2 weeks. The aim was to see how a neuro-oncology nurse offers psychosocial care to both patients and caregivers and how coordination and continuation of care are being provided. In France, there is no national oncology nursing programme. Compared to the Dutch Oncology Nursing Society with almost 3000 members, in France, the national oncology society counts about 200 members. Most French nurses end their jobs after 4–6 years, also because there are limited ways to develop their nursing function. This colleague successfully conducted a newly started advanced oncology programme for nurses with a duration of 12 months, provided by institutions in Marseille and Paris. Hopefully, the programme will be continued.

During her visit, we discussed ideas about the content of the nursing session and came to the conclusion that there is much knowledge to be obtained and spread for oncology nurses concerning neuro-oncology, despite the fact that in the past 10 years growing awareness has emerged within neuro-oncology care and cure – awareness of the needs of patients and their families in guidance throughout their disease concerning possible problems in coping, anxiety, fear, and depression, in obtaining access to care and cure with a low threshold in case of emergencies or sudden questions, and in shared responsibility in treatment and end-of-life decision-making. But what about the meaning (from a patient’s view) and the point (from a professional view) of rehabilitation, about end-of-life care, about cognitive disturbances and psychosocial disorders, cancer care disparities and patient access to health systems, clinical trials and effective cancer therapy, difficult ethical considerations in patients with a lack of insight? And last, but certainly not least, patient advocacy: what are the rights of a patient to obtain good care and information? To address all these topics, we have created a programme with a multidisciplinary character: nurses, a physiotherapist, a speech and language pathologist, a neuropsychologist, a psychologist, physicians and a patient advocate will be presenting, enabling the attending health care professionals to gain and share their knowledge and experience with each other.
Knowledge Enriches!

To increase access to education, EANO offers oncology nurses a parallel session during the biannual European neuro-oncology conference, which will be held in Marseille from September 6–9, 2012. It will take place on Friday, September 7, in Parc Chanot, Marseille. During this parallel nursing session, French translation will be available. Furthermore, the EANO website contains a special subsection for nurses – and other health care professionals – with interesting educational materials to advance and apply knowledge in neuro-oncology. A survey of psychosocial care of neuro-oncology patients in Europe to be found in this subsection will enlarge the insight of where we and our patients stand and could increase awareness of the need for neuro-oncology nurses. I would like to invite everyone who delivers psychosocial support to neuro-oncology patients to submit the completed survey to hannekezwinkels@eano.eu.

References:

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What You Don’t Know Won’t Hurt You ...

Kathy Oliver

... or will it?

Each year, 200,000 people worldwide develop a primary malignant brain tumour.

Although there are no statistics to show it, some of these people – as well as some of the tens of thousands of others who are diagnosed annually with low-grade, benign, and metastatic brain tumours – will want to know everything about their disease. The big picture, the truth, and nothing but the truth.

Others won’t want to know.

In their paper on “psychosocial and supportive-care needs in high-grade glioma”, the authors Catt, Chalmers and Fallowfield state: “Active information seeking is an integral part of coping strategies for both patient and their relatives” [1].

It is the strong belief of some brain tumour patients, caregivers, and advocates that patients must have as much information as possible about their disease, its genetic characteristics, existing treatments, and emerging experimental approaches if they are to make truly informed choices about their care.

What you don’t know can hurt you, they argue.

A fledgling pilot project in Britain has the potential to arm brain tumour patients with an unprecedented level of knowledge. It is a patient information portal which will give patients free access to data about their care held by the UK National Brain Tumour Registry (UK NBTR).

Dr Jem Rashbass, director of the UK NBTR, said: “The approach we propose will be incremental and designed to strengthen the relationship and deliver considerable benefits for both patients and their clinical teams. A key element of the brain tumour registry pilot will be to ensure that the technology, processes, and systems can easily be scaled to cover all cancer sites.”

Relying heavily on health information technology (“HIT” is “increasingly viewed as the most promising tool for improving the overall quality, safety and efficiency of the health delivery system” [2]), this potentially transformative project will give brain tumour patients pioneering access to aspects of their datasets.

These datasets generally include full-text pathology, multidisciplinary team data, Patient Administration System information (“PAS” data relates to hospital stays and activity), and some imaging. There is also data on radiotherapy, PET-CT imaging, vital status from the Office for National Statistics, and, from 2012, national chemotherapy data.

The pilot has the support of the National Brain Tumour Registry itself, the UK National Cancer Intelligence Network (NCIN), clinical groups, and a number of charities representing the UK brain tumour patient community.

The project’s steering group recognises that the initiative is not without controversy for it contains possible risks as well as benefits for patients who choose to participate.

Among the benefits are: upholding an individual’s rights to access their own healthcare data; empowering patients to take a more active role in their treatments and care, thus improving patient experience; driving up data quality and context (patients will be able to see, question, and comment on their own data); patients being better prepared to discuss their care with their clinicians; and the opportunity to contribute to the registry longer-term information about their brain tumour journeys which has the potential to improve not only treatment but quality of survivorship as well.

So it will not only be a case of asking what your brain tumour registry can do for you as the patient, but what you can also do for your brain tumour registry.

Among the risks are: fear and anxiety potentially inflicted upon patients by obtaining information which they may not easily understand or be able to appropriately interpret; the effects that patients being privy to this information may have on the clinician-patient relationship; and the potential for compromised security of personal data. The steering group recognises that in order to allay any fear and anxiety for the patient, most users of the portal will require information to be accompanied by professional interpretation so that medical terminology and data impact is correctly understood.

At the heart of this pilot programme are 2 important notions. The first is recognising patient ownership of their own medical data. The second is the notion of personal choice, a tenet which is enshrined in the UK NHS (National Health Service) Constitution [3]. It will be completely up to a brain tumour patient to choose whether he or she wishes to access their data on the brain tumour registry.

This innovative project is one of a number of emerging initiatives that focus on and support patients who wish to become experts in their own care.

Another such initiative – not brain tumour-specific but from which people with brain tumours can benefit – is the “European Patients Academy on Therapeutic Innovation” (EUPATI;
http://www.patientsacademy.eu). Launching in spring 2012 by a consortium of 30 partners led by patient organisations, this is a multi-million Euro programme which aims to educate patient advocates and the lay public about personalised and predictive medicine, design and conduct of clinical trials, drug safety, risk/benefit assessment, pharmaco-economics, and drug development. EUPATI will provide educational material in 6 European languages targeting 11 European countries [4].

Patient portals for rich but hitherto un-mined sources of data such as brain tumour registries, together with the opportunity to benefit from educational programmes such as EUPATI, have the potential to transform the brain tumour journey’s landscape.

References:

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# Calendar of Events

## 2012

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<tr>
<td>February 9-11</td>
<td>15th Biennial Canadian Neuro-Oncology Meeting</td>
<td>Vancouver, BC, Canada</td>
<td><a href="http://www.cbtc.ca">http://www.cbtc.ca</a></td>
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<tr>
<td>March 8-10</td>
<td>International Congress on Targeted Anticancer Therapies</td>
<td>Amsterdam, The Netherlands</td>
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<td>March 21-24</td>
<td>EBCC 8</td>
<td>Vienna, Austria</td>
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<td>March 31</td>
<td>Spring Meeting EORTC Brain Tumour Group</td>
<td>Brussels, Belgium</td>
<td><a href="http://groups.eortc.be/brain/">http://groups.eortc.be/brain/</a></td>
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<td>March 31-April 4</td>
<td>American Association for Cancer Research Annual Meeting</td>
<td>Chicago, IL</td>
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<td>April 25-28</td>
<td>3rd European Conference on Interventional Oncology</td>
<td>Florence, Italy</td>
<td><a href="http://www.ecio2012.org/">http://www.ecio2012.org/</a></td>
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<tr>
<td>April 26-17</td>
<td>8th European Oncology Nursing Society Spring Convention</td>
<td>Geneva, Switzerland</td>
<td><a href="http://www.ecco-org.eu/sitecore/content/Home/Conferences/Conferences/EONS%208">http://www.ecco-org.eu/sitecore/content/Home/Conferences/Conferences/EONS%208</a></td>
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<tr>
<td>May 9-13</td>
<td>ESTRO 31</td>
<td>Barcelona, Spain</td>
<td><a href="http://www.estro-events.org/Pages/ESTRO31.aspx">http://www.estro-events.org/Pages/ESTRO31.aspx</a></td>
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<tr>
<td>June 1-5</td>
<td>2012 ASCO Annual Meeting</td>
<td>Chicago, IL, USA</td>
<td><a href="http://www.asco.org">http://www.asco.org</a></td>
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<tr>
<td>June 4-8</td>
<td>13th Asian Oceanic Congress of Neurology</td>
<td>Melbourne, Australia</td>
<td><a href="http://www.aocn2012.com">http://www.aocn2012.com</a></td>
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<tr>
<td>June 9-12</td>
<td>22nd Meeting of the European Neurological Society</td>
<td>Prague, Czech Republic</td>
<td><a href="http://www.congrex.ch/ens2012">http://www.congrex.ch/ens2012</a></td>
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<td>June 21-24</td>
<td>19th International Brain Tumor Research and Therapy Conference</td>
<td>Niagara Falls, ON, Canada</td>
<td><a href="http://www.2012ibtrtc.ca">http://www.2012ibtrtc.ca</a></td>
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<td>June 30-July 3</td>
<td>International Collaborative for Brain Tumor Epidemiology</td>
<td>Montpellier, France</td>
<td><a href="http://epi.grants.cancer.gov/btec/">http://epi.grants.cancer.gov/btec/</a></td>
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<tr>
<td>July 7-10</td>
<td>EACR 22 Biennial Congress</td>
<td>Barcelona, Spain</td>
<td><a href="http://www.eacr.org">http://www.eacr.org</a></td>
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<tr>
<td>September 6-9</td>
<td>10th EANO Congress</td>
<td>Marseille, France</td>
<td><a href="http://www.eano2012.eu/index.php">http://www.eano2012.eu/index.php</a></td>
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<td>September 8-11</td>
<td>16th Congress of the European Federation of the Neurological Societies</td>
<td>Stockholm, Sweden</td>
<td><a href="http://www2.kenes.com/efns/pages/home.aspx">http://www2.kenes.com/efns/pages/home.aspx</a></td>
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<td>September 19-21</td>
<td>ESSO 2012</td>
<td>Valencia, Spain</td>
<td><a href="http://www.ecco-org.eu">http://www.ecco-org.eu</a></td>
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<td>September 28-October 2</td>
<td>37th ESMO Congress</td>
<td>Vienna, Austria</td>
<td><a href="http://www.esmo.org/events/vienna-2012-congress.html">http://www.esmo.org/events/vienna-2012-congress.html</a></td>
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<tr>
<td>October 4-6</td>
<td>48th Annual Meeting of the Austrian Society for Neurosurgery</td>
<td>Graz, Austria</td>
<td><a href="http://www.oegnc-jahrestagung.at">http://www.oegnc-jahrestagung.at</a></td>
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<tr>
<td>October 9-12</td>
<td>19th International Congress on Palliative Care</td>
<td>Montréal, Canada</td>
<td><a href="http://www.palliativecare.ca/">http://www.palliativecare.ca/</a></td>
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<td>October 13</td>
<td>Autumn Meeting EORTC Brain Tumour Group</td>
<td>Brussels, Belgium</td>
<td><a href="http://groups.eortc.be/brain/">http://groups.eortc.be/brain/</a></td>
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<td>November 6-9</td>
<td>Molecular Targets and Cancer Therapeutics</td>
<td>Dublin, Ireland</td>
<td><a href="http://www.ecco-org.eu">http://www.ecco-org.eu</a></td>
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<tr>
<td>November 15-18</td>
<td>17th Annual Scientific Meeting and Education of the Society for Neuro-Oncology</td>
<td>Washington, DC, USA</td>
<td><a href="http://www.soc-neuro-onc.org/2012/">http://www.soc-neuro-onc.org/2012/</a></td>
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## 2013

| May 9-12 | 19. Jahreskongress der Deutschen Gesellschaft für Radioonkologie | Berlin, Germany |
| May 31-June 4 | 2013 ASCO Annual Meeting              | Chicago, IL, USA | http://www.asco.org |

## 2014

| May 30-June 3 | 2014 ASCO Annual Meeting              | Chicago, IL, USA | http://www.asco.org |
| July 3-6      | 20. Jahrestagung der Deutschen Gesellschaft für Radioonkologie | Düsseldorf, Germany |
On November 5, 2011, the first Italian Association for Neuro-Oncology (AINO) and Association des Neuro-Oncologues d’Expression Française (ANOCEF) Joint Meeting was held in Milan during the 16th Annual Congress of the AINO. For the first time, a joint meeting between 2 national groups was organized with the purpose of bringing together leading experts from both countries to discuss similarities and differences in the approach of specific tumour types. Low-grade gliomas were chosen as the main topic and were addressed in all aspects from biology to treatment modalities within 4 sessions.

The meeting was opened by Marie de Tayrac (Rennes) with a lecture on, “Molecular profiling of gliomas”, illustrating the usefulness of a multi-dimensional integrated analysis to identify prognostic signatures.

In the first session, chaired by Carmine Carapella (Rome) and Marc Sanson (Paris), the role of molecular markers was addressed. Felice Giangaspero (Rome) illustrated the diagnostic contribution of molecular markers, such as p53 mutations, 1p/19q co-deletion, alpha-internexine expression, IDH1/2 mutations, or BRAF alterations to conventional neuropathological tools for differential diagnosis. Marc Sanson discussed the prognostic and predictive values of molecular markers in low-grade gliomas, particularly IDH-1/2 mutations, 1p19q co-deletion, and MGMT methylation/CIMP phenotype.

The second session, chaired by Jean Yves Delattre (Paris) and Massimo Scerrati (Ancona), was devoted to neuroimaging techniques. Andrea Falini (Milan) reviewed the role of MRI diffusion and DTI tractography for diagnosis, for predicting the extent of surgical resection, and for monitoring the response to chemotherapy. Alberto Bizzi (Milan) reported a prospective study on monitoring the eloquent areas for language with both fMRI and neuropsychological tests. Finally, Eric Guedj (Marseille) reviewed the role of old (FDG) and new (methionine, FLT) tracers for radiotherapy planning and monitoring the response to treatments.

The third session, chaired by Giovanni Broggi (Milan) and Xavier Muracciole (Marseille), addressed the role of surgery and radiotherapy. Lorenzo Bello (Milan) and Hugues Duffau (Montpellier) discussed the role of intraoperative use of brain mapping techniques (intra-operative monitoring and awake surgery) to maximize both the extent of resection and the functional integrity of eloquent areas. A survey on patterns of care within centres of radiotherapy in Italy and France was presented by Ugo De Paula (Rome), Laura Fariselli (Milan) and Xavier Muracciole. Particular attention was paid to the respective roles of radio- and chemotherapy as upfront treatment for high-risk patients after surgery.

The fourth session discussed the role of chemotherapy: Khê Hoang-Xuan (Paris) provided an exhaustive review of the state of art, while Roberta Rudà (Turin) and Luc Taillandier (Nancy) described the ongoing Italian and French studies on new strategies, such as dose-dense temozolomide, PCV and its sustained effect as a valuable alternative to TMZ, and pre-operative chemotherapy. Andrea Pace (Rome) addressed the topic of epilepsy, supportive care, and cognitive rehabilitation. The last talk (Costanza Papagno, Milan) was focused on quality of life and cognitive functions that are increasingly recognized as major endpoints in studies on low-grade gliomas.

Olivier Chinot (Marseille) and Riccardo Soffietti (Turin), chairmen of the last session, closed the meeting with the hope to strengthen, both in terms of future meetings and conjoint studies, the cooperation between the 2 countries. A joint session with AINO is planned at the next ANOCEF meeting in Clermond-Ferrand, France.

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The Dutch Society for Neuro-Oncology, or Landelijke Werk- groep Neuro-Oncologie (LWNO), has approximately 100 members, all physicians involved in the treatment of neuro-oncological patients, and 2 sub-committees for investigators (LWNO-i) and specialized nurses (LWNO-v).

The LWNO was founded in 1992; its main tasks are 4-fold.

- **Development and Maintenance of National Clinical Neuro-Oncological Guidelines and Treatment Protocols**

  The LWNO has developed guidelines on the diagnosis and treatment of gliomas, parenchymal brain metastases, leptomeningeal metastases, and spinal epidural metastases of solid tumours. A working group on a guideline on the diagnosis and treatment of meningioma has just been installed. All guidelines are revised every 5 years and in between if new scientific evidence with sufficient impact on the diagnosis and/or treatment emerges. The guidelines are accessible through the website “Oncoline” (http://www.oncoline.nl), the digital oncological guideline database of the Dutch Cancer Centre (IKNL). A part from those guidelines, the LWNO has developed treatment protocols for rare tumours such as medulloblastoma and germ cell tumours in adults.

- **Development of Quality Criteria for Care of Neuro-Oncological Patients**

  In close collaboration with Dutch advocacy groups of patients with neurological diseases and patients with cancer, the LWNO currently works on a document that defines qualitative and quantitative criteria for adequate care for neuro-oncological patients. These criteria will involve definitions of a sufficiently equipped hospital brain tumour multidisciplinary board and multidisciplinary outpatient clinic. A part from that, we will provide guidelines for maximum intervals between diagnosis and start of treatment, and minimal numbers of patients to be treated. This document will set the stage for further improvement of the quality of care for this patient group throughout the Netherlands.

- **Support of National Clinical and Pre-Clinical Neuro-Oncological Studies**

  Dutch neuro-oncology has a longstanding reputation of excellent research, and members of the LWNO have played, and still play, important roles in international neuro-oncological societies and research organisations, such as EANO, EORTC, and SNO. A part from those international collaborations, which the LWNO actively endorses, the LWNO provides support and a forum for the set-up of national clinical and preclinical studies, such as a randomised phase-II study on bevacizumab vs lomustine vs bevacizumab/lomustine in recurrent glioblastoma (BELOB study) and a randomised study on the internet-based treatment of glioma patients with depression.

- **Providing a National Forum**

  The LWNO provides a national forum for medical professionals involved in the research and treatment of neuro-oncological patients. The LWNO organizes meetings, such as our annual scientific meeting and the regular plenary meetings as well as meetings of the specific working groups and subcommittees. At the annual scientific meetings, the “STOPHersentumoren.nl” and the “Ties Rudolphie” prizes are awarded to outstanding professionals in neuro-oncology. On an ad hoc basis, the LWNO advises Dutch governmental and health organisations on neuro-oncological issues.

For more information please contact us via e-mail (vandekar@planet.nl) or visit our website (http://iknl.ecommany.com/Landelijk/werkgroepen/no_voor_leden/index.php).

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Q: Can you tell us about the ongoing "Elderly Glioblastoma" trial? What is the rationale and background for this trial?

A: Thank you for giving us the forum to discuss this international cooperative group study that addresses an important unmet need in the management of older patients with glioblastoma. We know from the EORTC/NCIC-CTG study that the addition of concurrent and adjuvant temozolomide (TMZ) to standard radiotherapy (60 Gy/30 fx) clearly improves survival [1]. However, a trend-benefit analysis by the EORTC found decreasing benefit with increasing age. We do not know if this was due to the size of the subgroup of elderly patients in the trial (and therefore a problem with statistical power) or if there is truly less benefit seen with increasing age. Therefore, a randomized trial testing the same clinical question (RT ± concurrent and adjuvant TMZ) was proposed for newly diagnosed elderly patients. We learned from the Roa et al trial that 40 Gy/15 fractions (ie, 3 weeks) of radiotherapy appears to give similar survival results to 60 Gy/30 fractions in the elderly [2]. We also learned from the ANOCEF trial that so-called “short-course” radiotherapy plus supportive care is superior to supportive care alone [3]. Therefore, this trial was built around the central premise that many older patients are given short-course radiotherapy in brain tumour centres across the world; yet we do not know if the addition of concurrent and adjuvant TMZ is of benefit.

Q: What are the design and inclusion criteria?

A: This is a randomized phase-III trial for patients over the age of 65 with newly diagnosed glioblastoma. Local pathological diagnosis is sufficient for study randomization but tissue is being collected for molecular companion analyses, especially determination of MGMT promoter methylation status. Patients are stratified within predefined age groups, by PS, and by centre. There was one planned interim futility analysis and the independent DSMB has recommended proceeding with the trial.

Q: What is your definition of the elderly? Why did you choose 65 as cut-off?

A: Initially we designed this study with age restricted to 70 and above. This “pure” approach would therefore not overlap with patients who were in the previous EORTC/NCIC-CTG study and for whom level-1 evidence suggests treatment with “full-course” radiation plus chemotherapy. However, we felt that the statistical power of the results over the age of 65 left the 65–70-year-old age group in an uncertain category and, after discussions with colleagues at the EORTC Brain committee, we came to realize that many centres use short-course radiotherapy routinely over the age of 65. So this became a pragmatic point in terms of maximizing accrual opportunity. To date, the median age of patients in the study is 73 years; so we believe that we are collecting an older cohort of patients (¼ is 65–70, ¼ is 71–75, and ¼ is > 75). It is important to remember that the central question of this study is to test whether or not the addition of chemotherapy is important for patients who are recommended short-course radiation therapy. We expect that some centres will continue to offer 60 Gy/30 fractions to suitably fit patients between 65 and 70; so this study requires and allows for clinical judgement of the best radiotherapy prescription on a case-by-case basis.

Q: Which groups, countries, and how many centres participate in the trial?

A: The study is led by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) with major participation from the EORTC, the Trans-Tasman Radiation Oncology Group (TROG), Japan, and most recently by the new American cooperative group (ACTION). A accrual to date is NCIC-CTG 17 sites, n = 135; EORTC 27 sites, n = 122; TROG 14 sites, n = 53, and Japan 2 sites, n = 6.

Q: Recent results from the German NOA-8 and Nordic trials showed somehow contradictory results on first-line treatment with radiotherapy or temozolomide [4, 5]. Taking into account those 2 other trials, how will your trial answer the question of treatment for this population? Would you prefer to have a third arm with temozolomide alone within the trial?

A: These 2 important clinical trials did not show superiority of radical radiotherapy in newly diagnosed elderly patients with glioblastoma. Taken together with prior radiotherapy studies in the elderly we feel it is now reasonable to consider shorter-course radiotherapy (such as 40 Gy/15 fx) as standard of care. These results fortuitously make the study question in our trial an important one. Our ongoing study will be the first to test the efficacy and toxicity of concurrent and adjuvant TMZ added to this radiation scheme. We initially included a chemotherapy-alone arm; however, this resulted in a very large sample size and, at that time, would have conflicted with the ongoing European trials.

Q: Do you have any translational or biological investigation in this trial?

A: Tissue is being collected and a full translational analysis will be coordinated and conducted through the NCIC-CTG headquarters in Kingston, Ontario, Canada.

Q: How is the accrual and when do you expect to reach the accrual goal? When can we get the first results?
**Ongoing Trials**

**A:** The addition of the EORTC provided a meaningful increase in accrual and we anticipate the participation of US centres in early 2012. In order to have 90-% power to detect a 25-% increase in the primary outcome of overall survival (increased MST from 6 to 8 months) between arms, using a 2-sided 5-% alpha, a minimum of 520 deaths must be observed prior to analysis. Total sample size is 560. As of September 30, 2011, there were 316 patients randomized. The accrual rate is approximately 10–12 per month at present, so we estimate the trial will complete accrual by the end of 2013.

Thank you very much!

James Perry is NCIC-CTG study co-chair (along with Dr Normand Laperriere) for the trial entitled “A randomized phase III study of temozolomide and short-course radiation versus short-course radiation alone in the treatment of newly diagnosed glioblastoma multiforme in elderly patients”.

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**Hotspots in Neuro-Oncology**

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

- **Peri-Ictal Pseudoprogression in Patients with Brain Tumor**

  In the July issue of *Neuro-Oncology*, another chapter was published on the ongoing controversy of pseudoprogression as a confounding factor when monitoring response to therapy. Rheims and colleagues reported on a series of 10 brain tumor patients who experienced pseudoprogression in the context of epileptic seizures. These interesting observations in a small number of patients illustrate the need to carefully assess changes in the MRI scans shortly after epileptic seizures in order to avoid the false diagnosis of progression.

- **A Small-Molecule IAP Inhibitor Overcomes Resistance to Cytotoxic Therapies in Malignant Gliomas In Vitro and In Vivo.**

  The August issue experienced a potential comeback of a cytotoxic therapy approach to malignant glioma that attracted a lot of interest a few years ago, but gained much less attention more recently. Inhibitors of apoptosis proteins (IAP) are among the cellular defence mechanisms to prevent the biochemical cascade of apoptosis involving caspase activation. It has been tried to block cytoprotective IAP function in various cancer models including gliomas, using different agents and delivery approaches. Here, Ziegler and colleagues demonstrate that the systemic treatment with a small-molecule IAP inhibitor is feasible and active, in the apparent absence of significant toxicity.

- **Infratentorial Craniospinal Irradiation for von Hippel-Lindau: a Retrospective Study Supporting a New Treatment for Patients with CNS Hemangioblastomas**

  Treatment options for patients with von Hippel-Lindau disease with diffuse CNS hemangioblastomas are very limited. This report of 7 patients with 84 hemangioblastomas indicates that infratentorial craniospinal irradiation to 43.2 Gy in 24 fractions offers a potentially reasonable treatment strategy with complete resolution of some lesions and a decrease in the growth rate and surgical interventions compared with historical controls.

- **Morbidity and Mortality Following Acoustic Neuroma Excision in the United States: Analysis of Racial Disparities During a Decade in the Radiosurgery Era**

  This article from the November issue is among the most provocative articles published in *Neuro-Oncology* in 2011. In essence, data from a nationwide inpatient sample from 1994-2003 revealed a postoperative mortality rate following acoustic neuroma surgery of 0.5% and of an adverse discharge disposition of 6.1%. Patients had a better outcome when they were operated by high-caseload surgeons, had private insurance, and were younger. There was a significant increase of risk of death among African Americans. These data call for reconsiderations of the current patterns of care of acoustic neuromas in the US (and also for similar analyses in other countries throughout the world).

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The Society for Neuro-Oncology’s 16th Annual Scientific Meeting and Education Day took place November 17–20, 2011, in Anaheim, California. In addition to the scientific and educational sessions, there were several important international committee meetings at which members discussed efforts to increase cooperation between the various national and regional neuro-oncology organizations as well as initiatives to provide outreach to developing regions of the world.

The first of these sessions was the inaugural meeting of the World Federation of Neuro-Oncology Societies (WFNOS). This new organization seeks to improve communication between neuro-oncology societies and to coordinate and formalize the planning process for future quadrennial World Federation of Neuro-Oncology (WFNO) conferences. The session enjoyed broad international participation, with representatives from North America, Europe, Japan, Korea, Australia, India, and China. As an initial first step, it was agreed that a charter should be drafted to outline the relationship between the organizations as well as to codify a transparent process for selecting the locations for future WFNO meetings. It was generally accepted that the location of WFNO meetings should rotate between North America, Europe, and Asia every 4 years, and that there should be inclusive international representation within the scientific planning committee. The charter is currently being drafted and will be ready for dissemination to the member organizations in early 2012. The next WFNO meeting will take place November 20–24, 2013, at the Marriott Marquis Hotel in San Francisco, California.

With the goal of improving clinical and research activities in the management of children and adults with brain tumours in developing regions of the world, the SNO International Outreach Committee held an informative lunchtime session addressing the global disparities that exist in neuro-oncology care and treatment. Topics discussed included “Care in the Middle East” (Mark Kieran), “Neuro-Oncology in Iraq” (Mustafa Khasraw) and “Teleconferencing in North Africa” (Eric Bouffet). A highlight of the session was the introduction of Dr Jun-Ping Zhang, the recipient of the 2011 SNO International Outreach Fellowship. Through a competitive application process, this fellowship provides a US$ 50,000 award to an individual from a low-income or developing country to travel to the United States or Canada to study at a leading academic institution. Dr Zhang, a Chinese national, will be mentored by Dr Patrick Wen at the Dana-Farber Cancer Institute in Boston, Massachusetts. Applications for the 2012 International Outreach Fellowship are now being accepted, and members of EANO are encouraged to refer potential applicants to the SNO website.

http://www.soc-neuro-onc.org/international-outreach/

The deadline for applications is February 3, 2012.

Looking ahead, planning is now underway for a special supplemental issue of our official journal, Neuro-Oncology, that will focus on applied neuro-oncology and the practical aspects of the care and treatment of patients with brain tumours. This exciting new initiative seeks to provide a forum for international collaboration and an opportunity to share experiences across the various societies. The special issue will highlight the importance of evaluating the effects that the diagnosis and treatment of brain tumours have on patients and caregivers with respect to clinical factors other than survival, and the critical need to study this systematically through prospective research efforts. Susan Chang will serve as editor-in-chief of the supplement, with the assistance of co-editors from each of the participating societies: Masao Matsutani (ASNO), Riccardo Soffietti (EANO), and Jeffrey Wefel (SNO). The co-editors will be responsible for soliciting the papers from their respective societies, with the goal of having the special issue completed in time for the next SNO meeting scheduled for November 15–18, 2012, at the Hilton Hotel in Washington, DC.

Finally, in an effort to further promote international education and exchange, SNO and EANO are organizing reciprocal “meet the expert” sessions at their respective meetings in 2012. A competitive application process for travel grants for young investigators will also be initiated in the New Year, and details will be posted shortly on the SNO and EANO websites.

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http://www.soc-neuro-onc.org
Instructions for Authors

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Dedicated to providing superior and rapid publication of information in all areas of neuro-oncology, this education-oriented journal contains peer-reviewed articles and reviews, case reports, congress reports, letters, society news and announcements from around the world with a special focus on Europe and the EANO member states.

Aims of the EANO Neuro-Oncology Online Magazine is to provide the European neuro-oncology community, in particular of the EANO member states, with high-quality rapid publication of information in all fields of neuro-oncology via open online access.

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