

European Association of NeuroOncology Magazine

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EDITORIAL

Riccardo Soffietti

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Marc C Chamberlain

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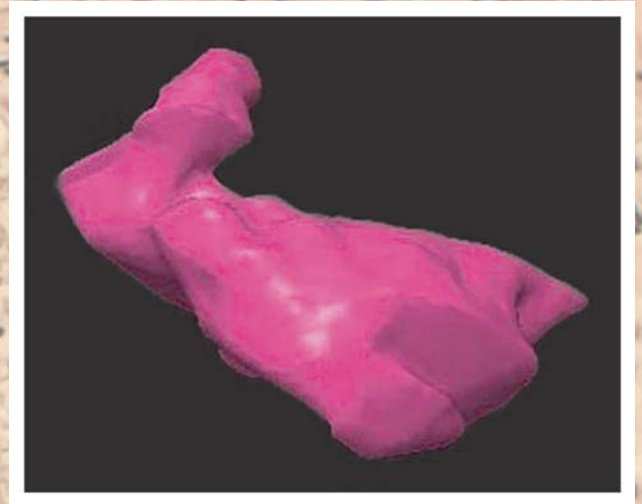
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European Association of NeuroOncology Magazine



ISSN-Online: e-ISSN 2224-3453

Official Organ of the European Association of Neurooncology

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Publisher's Office:

Krause & Pachernegg GmbH
Mag. Irene Schinnerl
e-mail: irene.schinnerl@kup.at
Verlag für Medizin und Wirtschaft
3003 Gablitz, Mozartgasse 10, Austria
Tel. +43/2231/61258-0, Fax +43/2231/61258-10

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Editorial

Dear colleagues,

before moving on to the new initiatives of EANO in 2013, I want to inform you regarding two events that took place in the final months of 2012. The first was the Oncopolicy Forum 2012, organized by ECCO in Brussels in October, consisting of a 1-day meeting on “the Future of Personalized Cancer Medicine in Europe”. The chairmen of oncologic societies (including EANO), major cancer centres, and patient organizations met with representatives of the European Commission for Research, Innovation and Science and health economy experts to discuss how to improve the organization of research, education, and ethical issues within Europe. Three major needs emerged: (1) the need for a central authority in the EU to work on quality assurance of new diagnostic and imaging techniques to uniform validation and reimbursement procedures, (2) the need to define centres of excellence for a future multidisciplinary personalized cancer medicine, and (3) the need of patients as partners for research, especially in rare diseases. All these issues are among the objectives that we are pursuing. The second event I want to inform you about is the meeting of the new EANO Executive Board (elected in Marseille in September) in Frankfurt in December, where we defined the actions to be taken in 2013. We reached a final agreement on several administrative issues such as tax payment and secretariat activities. In particular, from January the Vienna Medical Academy, ie, the agency organizing our meetings, will act as EANO secretariat as well. We will soon move to a final update of the bylaws which will be circulated among members for definitive approval. New task forces to develop guidelines on malignant gliomas, primary central nervous system lymphomas, and brain metastases are being organized.

In 2013, EANO will be directly involved in the organization of two international meetings. The first will be held in Prague from March 22–23 and comprise an update on the major issues under discussion in the neuro-oncological field. The second, probably most important event will be the 4th Quadriennial Meeting of the World Federation of Neuro-Oncology in San Francisco from November 21–24. In this regard, we are actively working together with colleagues from SNO (US) and ASNO (Japan) to define the structure of the World Federation of Neuro-Oncology. Notably, at the beginning, national groups from various areas of the world could apply.

Last but not least, the EANO Magazine and the website are going very well and I would like to invite any individual member to contribute cases, news, or any other material (by contacting Dr Wolfgang Grisold or Dr Khê Hoang-Xuan).

My best wishes for a Happy and Productive New Year!

Riccardo Soffietti, MD

EANO President (2012–2014)



Riccardo Soffietti, MD



Prognostic Utility of Neuraxis Imaging in Leptomeningeal Metastasis: A Retrospective Case Series

Marc C Chamberlain

Abstract: *Objective:* Correlate imaging and survival in a retrospective series of patients with leptomeningeal metastasis (LM).

Methods: 240 patients with LM (125 solid tumour patients with positive CSF cytology; 40 solid tumour patients with negative CSF cytology and MRI consistent with LM; 50 lymphoma and 25 leukaemia patients with positive CSF flow cytometry), all considered for treatment, underwent prior to treatment neuraxis MRI and radio-isotope CSF flow studies.

Results: Survival was significantly shortened in patients with large volume MRI-defined disease and in patients with CSF flow obstruction irrespective of primary tumour histology. Additionally, cause of death differed wherein patients with large volume of disease or obstructed CSF flow more often died of progressive LM disease.

Conclusions: Neuraxis imaging utilizing brain and spine MRI as well as radio-isotope CSF flow studies has prognostic significance and is

predictive of median overall survival in this large cohort of patients all considered for treatment with LM. **Eur Assoc NeuroOncol Mag 2012; 3 (1): 6–10.**

Key words: leptomeningeal metastasis (LM), neuraxis imaging, brain and spine contrast MRI, CSF radio-isotope flow study, survival

Introduction

Leptomeningeal metastasis (LM) is the third most common central nervous system (CNS) metastatic complication of cancer occurring in 2–5 % of all patients with solid tumour cancers [1–8]. There is general agreement that in patients considered for LM-directed therapy, CNS staging is indicated as for example articulated in the CNS tumour section of the National Comprehensive Cancer Network guidelines [8]. However, there is limited consensus regarding the extent of CNS imaging required to assess a patient with LM prior to treatment as there have been few studies that correlate CNS imaging abnormalities with survival in patients with LM and consequently the relevance of imaging is unknown. At present, there are no large prospective or retrospective studies that have compared results of pre-treatment imaging with survival in patients with LM [9–23]. This retrospective case series of 240 patients with solid tumours (exclusive of primary brain tumours) and haematological cancer-related LM correlates brain and spine MRI findings as well as radio-isotope CSF flow study findings prior to treatment with overall survival in patients considered eligible for LM-directed therapy.

Methods

Patient Population

The retrospective analysis commenced in January 1987 and closed in December 2011. 240 adult patients with a median age of 58 years (range 20–86) with LM defined by CSF positive for cancer (defined as positive or suspicious by cytopathology; atypical was considered negative) with one patient group exception (solid cancers with negative CSF cytology;

vide infra) were evaluated and considered for LM-directed treatment (Table 1). The intent in all patients was to proceed with intra-CSF chemotherapy and CNS site-specific radiotherapy or systemic chemotherapy when clinically appropriate. Patients with LM defined clinically and with negative CSF cytology or flow cytometry and normal neuraxis imaging and patients with primary brain tumours were not included in this retrospective imaging analysis. Approximately two thirds of the current patients have previously been reported in other contexts not however specifically addressing pre-treatment neuroimaging findings or correlation with survival [24–31]. In addition to excluding patients with negative CSF cytology or flow as well as normal neuraxis MR imaging, patients not considered candidates for LM-directed treatment (defined by a low Karnofsky performance status < 60; expected limited survival, and progressive systemic disease) were not evaluated in this analysis. One category of solid tumour-related LM considered in the analysis was defined by an LM compatible clinical syndrome, negative CSF cytology, and neuraxis imaging demonstrating radiographic abnormalities consistent with LM. All but 25 patients (8 solid tumours, 17 haematologic malignancies) were symptomatic with signs and symptoms of LM.

All patients underwent a similar pre-treatment LM evaluation including CSF assessment (cytology for solid tumours or flow cytometry and cytology for haematological cancers), contrast-enhanced brain and entire spine MR imaging, and radio-isotope ¹¹¹-Indium CSF flow study as previously reported [9–23]. LM was confirmed in all patients (except for a group of 40 patients with solid cancer and radiographic-only LM) by either positive CSF cytology (in instances of solid tumours and haematologic cancers) or flow cytometry (in haematologic cancers). A majority of patients (85 %) had an Ommaya ventricular access device implanted to facilitate administration of intra-CSF chemotherapy.

The primary tumour histology in patients with solid tumour-related LM (n = 165; 69 % of all patients in the analysis) was breast (45 %) and non-small cell lung cancer (34 %) (Table 1).

Received on November 21, 2012; accepted after revision on December 12, 2012; Pre-Publishing Online on December 18, 2012
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No primary brain tumours were considered in this retrospective study. Haematologic cancers (n = 75; 31 % of all patients in the analysis) were comprised of lymphoma (n = 50; 75 % of all patients with haematologic cancer of which 80 % were diffuse large B-cell lymphoma) and leukaemia (n = 25; 25 % of all patients with haematologic cancer of which 64 % were AML). Karnofsky performance status ranged from 60–100 with a median of 80.

Data Collection

Data regarding CNS evaluation (brain and spine MRI; CSF flow studies) obtained before any LM-directed treatment and patient characteristics was prospectively collected and entered into a database. Institutional review board approval was obtained for data collection as well as patient consent for all prospective data collection. No institutional or corporate funding was provided for this analysis.

Imaging

Magnetic Resonance (MR) Imaging

All patients underwent complete neuraxis magnetic resonance imaging (MRI; brain and complete spine) using standard sequences (T1-weighted, T2-weighted, and FLAIR) and pre- and post-contrast imaging as previously described [9–13, 19]. MR imaging was performed on either a 1.5 or 3.0 Tesla MRI machine. Hydrocephalus was noted as present or absent to permit coding of radiographic abnormalities. Contrast enhancing nodules were characterized as subarachnoid (defined as nodules in the CSF containing subarachnoid space), ventricular, or parenchymal (defined as nodules within brain parenchyma) and as present or absent. In addition, nodular disease was characterized as either < or > 5 × 10 mm in orthogonal diameters. Using these parameters, patients with LM and tumour nodules in any location (brain or spine parenchyma or subarachnoid space or ventricular) were subdivided into small or large volume LM disease. Pial enhancement was defined as focal, diffuse, or none. Other abnormalities characterized and tabulated were ependymal, sulci, folia, cranial nerve, or spinal root enhancement as either present or absent.

Table 1. Patient characteristics

Characteristics	Solid tumour Cytology negative	Solid tumour Cytology positive	Lymphoma Flow cytometry positive	Leukaemia Flow cytometry positive
n	40	125	50	25
Age (years)				
Median	56	58	60	62
Range	20–71	32–78	30–86	31–82
Male/female (%)	52/48	60/40	50/50	56/44
Karnofsky Performance Status				
Median	80	70	80	80
Range	50–100	50–100	50–100	50–100
Symptomatic				
No	18 % (7)	0 %	5 % (3)	15 % (4)
Yes	72 % (33)	100 % (125)	95 % (47)	85 % (21)
Tumour histology				
Breast	45 % (18)	45 % (56)		
NSCLC	30 % (11)	35 % (44)		
Melanoma	15 % (6)	10 % (13)		
SCLC	5 % (2)	5 % (6)		
Other	10 % (3)	5 % (6)		
DLBCL			80 % (39)	
Follicular lymphoma			10 % (5)	
Mantle cell lymphoma			5 % (3)	
Burkitt's lymphoma			5 % (3)	
AML				64 % (16)
ALL				20 % (5)
CLL				10 % (2)
CML				10 % (2)

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; DLBCL: Diffuse large B-cell lymphoma; AML: Acute myelogenous leukaemia; ALL: Acute lymphoblastic leukaemia; CLL: Chronic lymphocytic leukaemia; CML: Chronic myelogenous leukaemia

Radio-Isotope CSF Flow Studies

All patients underwent either lumbar or ventricular administered ¹¹¹-Indium DTPA CSF flow studies prior to treatment and as previously described [9, 14–18, 20–23]. Failure of radio-isotope movement was defined as complete obstruction or blockage of CSF flow. The site of CSF flow interruption was identified as either in brain (ventricular, skull base, or convexity) or spine (cervical, thoracic, or lumbar). Partial CSF flow obstruction was not considered as constituting a CSF flow block. In the event CSF flow obstruction was identified, site of obstruction directed radiotherapy (30 Gy in 10 fractions) was administered. Patients were categorized as normal (no obstruction) or abnormal (obstruction present) with respect to CSF flow obstruction. In patients with obstruction, a repeat CSF flow study was performed following site-directed radiotherapy and patients were categorized as normal (termed re-established) or abnormal (obstruction persists) with respect to CSF flow obstruction.

Therapy

Intra-CSF chemotherapy using a variety of agents but predominantly liposomal cytarabine and administered by the intraventricular route was given to > 85 % of all patients as previously described [23–31]. Site-specific radiotherapy (to sites of symptomatic disease, to MRI defined large volume disease and to sites of CSF flow obstruction) was administered to

45 % of patients. Systemic chemotherapy was used in the majority (90 %) of patients with haematological cancers and in approximately 27 % of solid tumour-related LM patients.

Survival Analysis

Overall survival (OS) was defined as the time from LM diagnosis to death or last follow-up when patients were still alive. Survival rates were determined using the Kaplan Meier method and survival curves were compared using the log-rank test. Statistical analysis were performed using the SAS Software (USA, Cary, NC) V9.2.

Results

Four categories of patients with LM were retrospectively analyzed; solid tumour-related LM with (n = 125) or without (n = 40) positive CSF cytology, lymphoma (n = 50), and leukaemia (n = 25; Table 2). Both categories of haematologic cancers (lymphoma and leukaemia) were positive by CSF flow cytometry and in 40 % positive as well by CSF cytology. In 4 patients (5 % of all patients with haematologic cancers) with haematologic malignancies CSF flow cytometry was negative and LM was determined by CSF cytology.

Patient categories were further divided into normal or abnormal MRI findings (Table 2). Abnormal MRI findings were then divided into small or large volume disease as defined by measurable tumour nodules < or > 5 × 10 mm in orthogonal diameter. Solid tumour-related LM had a higher incidence of patients with abnormal MRI findings as well as patients with large volume disease as compared to haematological cancer-related LM. Patients were also characterized by having normal or abnormal (ie, obstructed) radio-isotope CSF flow studies. One further category included patients with initial obstructed CSF flow that following radiotherapy converted to normal CSF flow (re-established) as determined by post-radiotherapy CSF flow study (Table 2).

Median overall survival (mOS) was similar (p = 0.3) in both categories (CSF positive and CSF cytology negative) of patients with solid tumour-related LM (Table 3). However, survival in patients with solid tumour-related LM with large volume disease was significantly less than in patients with either normal MRI findings or small volume disease (p = 0.03). Similarly, mOS was not significantly different in solid tumour patients with normal or re-established CSF flow studies (p = 0.2). There was a significant difference in patients with ob-

Table 2. CNS imaging

Pre-treatment imaging	Solid tumour		Lymphoma	Leukaemia
	Cytology negative	Cytology positive		
n	40	125	50	25
MRI (brain + spine)				
Abnormal	40 (100 %)	50 (40 %)	10 (20 %)	4 (16 %)
Small volume disease	10 (25 %)	25 (50 %)	8 (80 %)	3 (75 %)
Large volume disease	30 (75 %)	25 (50 %)	2 (20 %)	1 (25 %)
Normal	0 (0 %)	75 (60 %)	40 (80 %)	21 (84 %)
CSF flow study				
Abnormal	10 (25 %)	35 (28 %)	5 (10 %)	2 (8 %)
Re-established	4 (40 %)	12 (34 %)	2 (40 %)	1 (50 %)
Normal	30 (75 %)	90 (72 %)	45 (90 %)	23 (92 %)

Small volume disease: number of patients (percent) with MRI abnormalities and without tumour nodules or nodules < 10 mm in diameter; Large volume disease: number of patients (percent) with MRI abnormalities and tumour nodules > 5 × 10 mm in diameter; Abnormal: number of patients (percent) with obstructed CSF flow study; Re-established: number of patients (percent of total obstructed) post-radiotherapy with normal CSF flow study

Table 3. Median overall survival with respect to CNS imaging

Pre-treatment imaging	Solid tumour		Lymphoma	Leukaemia
	Cytology negative	Cytology positive		
n	40	125	50	25
MRI (brain + spine)				
Abnormal				
Small volume disease	3 months	3.5 months	5 months	6 months
Large volume disease	2 months	2 months	3 months	2 months
Normal	3 months	3.5 months	5 months	6 months
CSF flow study				
Abnormal	2 months	2 months	2 months	2 months
Re-established	3 months	3.5 months	5 months	6 months
Normal	3 months	3.5 months	5 months	6 months

structed (abnormal) CSF flow that could not be corrected by radiotherapy compared to the other 2 categories (normal or re-established; $p = 0.04$).

Comparable findings were seen with haematological cancer-related LM wherein normal or small volume MRI abnormalities defined a longer surviving cohort of patients relative to patients with large volume disease ($p = 0.018$). In addition, CSF obstruction not corrected by radiotherapy characterized a haematological cancer patient category with worse outcome than those with normal or re-established CSF flow studies ($p = 0.015$).

Cause of death, an arguably subjective analysis, showed similar trends across all categories of patients wherein patients with either large volume disease defined by MRI or non-corrected CSF flow obstruction by radio-isotope imaging more often died of LM (2-fold increase) compared to patients with normal or small volume MRI disease and normal or re-established CSF flow (Table 4). By contrast, patients with normal or small volume MRI disease and normal or re-established CSF flow more often (3-fold increase) died of systemic disease progression.

■ Discussion

It has previously been suggested that there are categories of patients with LM that are not candidates for LM-directed therapy [8]. As outlined in the NCCN CNS tumour guidelines *vide supra*, these include patients with poor performance, likely short life expectancy, carcinomatous encephalopathy, uncorrected CSF flow obstruction, and large CNS tumour burden [8]. These recommendations are primarily based upon expert opinion with a paucity of literature-based evidence. The current retrospective study selected patients considered eligible for LM-directed therapy based upon these recommendations and excluded patients *a priori* not considered by clinical criteria to warrant intra-CSF chemotherapy. What remains problematic in treating patients with LM is deciding whom to treat and the current large retrospective study provides some illumination in this regard.

Previous work has suggested CSF flow studies are informative with respect to outcome and the current study corroborates these findings in a considerably larger patient data set [14–18, 20–23]. CSF flow obstruction as defined by radioisotope studies appears prognostic as patients with non-corrected CSF flow obstruction survive a significantly shorter time than patients with normal or re-established CSF flow irrespective of tumour histology (solid tumour or haematological cancer-related LM). In part the impoverished survival seen in patients with CSF flow obstruction is reflective of tumour burden as well as the pharmacologic barrier posed by interrupted CSF flow dynamics that mitigates intra-CSF chemotherapy administration. Whether intra-CSF chemotherapy alters survival in patients with LM is as yet undetermined and controversial as there has never been a large prospective randomized trial that shows a survival benefit for the receipt of intra-CSF chemotherapy [32, 33]. In that CSF flow obstruction was not predicted by MRI aside from the finding of hydrocephalus (nor by patients presenting symptoms) in the current study (data not shown), radio-isotope CSF flow studies appear complimentary to MRI in determining outcome in patients otherwise considered for LM-directed therapy. The current study supports the paradigm of utilizing CSF flow studies in patients with LM considered for treatment regardless if intra-CSF chemotherapy is used as survival is negatively impacted with evidence of interrupted CSF flow. Importantly, the current findings, ie that CSF flow obstruction is prognostic, require validation in a prospective study of LM wherein radio-isotope CSF flow studies are incorporated into pre-treatment evaluation. It was also noted that patients with non-correctable CSF flow obstruction more often succumb to LM as a cause of death than patients with normal or re-established CSF flow. Though the current study represents the largest data set of patients with haematological cancer-related LM ($n = 75$), the total number of patients, particularly with obstructed CSF flow, is comparatively small ($n = 7$) and therefore may not be generalizable.

MRI-based imaging in patients with LM has primarily been utilized to define brain involvement and when spine MRI is used, its use is mostly to define clinically site-relevant disease involvement [10–13]. The current study is unique in defining

Table 4. Cause of death with respect to CNS imaging

Pre-treatment imaging	Solid tumour						Lymphoma			Leukaemia		
	Cytology negative			Cytology positive								
n	40			125			50			25		
Cause of death (%)	LM	SD	LM + SD	LM	SD	LM + SD	LM	SD	LM + SD	LM	SD	LM + SD
MRI (brain + spine)												
Abnormal												
Small volume disease	23	53	25	25	48	27	26	51	25	24	52	23
Large volume disease	48	15	37	53	12	35	47	16	37	51	14	35
Normal	25	51	24	23	55	22	24	52	24	25	50	25
CSF flow study												
Abnormal	51	14	35	47	16	37	53	12	35	48	15	37
Re-established	25	50	25	25	50	25	25	50	25	25	50	25
Normal	25	50	25	25	50	25	25	50	25	25	50	25

LM: leptomeningeal metastasis; SD: systemic disease; LM + SD: combined LM and systemic disease

the total burden of CNS disease in patients with LM as all patients underwent both brain and whole spine MRI. Although the data is not shown, there was limited concordance between symptoms and MRI findings whether in brain or spine. Consequently, CNS disease burden is not predicted by LM-related symptoms and therefore neuraxis imaging is required to adequately stage the CNS. More important, however, is the correlation between survival and MRI-defined disease burden. In patients with large volume disease defined in this study as patients with tumour nodule(s) $> 5 \times 10$ mm in size, survival is significantly shortened relative to patients with normal or small volume MRI disease. Whether tumour nodules $> 5 \times 10$ mm in diameter define all categories of large tumour burden is unknown as there has never been a study attempting to quantify LM disease burden. Five by 10 millimetre diameters were selected as nodules of this size or larger were easily and reproducibly measured by MRI. Other common radiologic findings by MRI of LM for example leptomeningeal, cranial nerve, or spinal nerve root enhancement do not lend themselves to quantification. An improved radiographic method to quantify LM disease burden would be a welcome tool in assessing LM disease. Also noted in patients with large volume disease burden, cause of death was more often a result of LM as compared to patients with normal or small volume MRI disease that more frequently died due to systemic disease progression.

In conclusion, neuraxis imaging utilizing brain and spine MRI as well as radio-isotope CSF flow studies may have prognostic significance and appears predictive of median overall survival in this large cohort of patients with LM. The study is limited by the retrospective design, the novel definition of MRI large volume disease, and multiple small categories of patients upon which these conclusions are based. However, pending a larger prospective trial the current retrospective data set is the most robust data available regarding the utility of CNS imaging in predicting survival in patients with LM.

Conflict of Interest

The author has no financial disclosures.

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Surgery of Malignant Gliomas Using Modern Technology

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Abstract: Recent evidence has demonstrated that the extent of surgical resection (EOR) is an important prognostic factor in patients with malignant gliomas. However, the infiltrative growth pattern and the functional anatomy of the brain consisting of eloquent cortical and subcortical structures pose a significant limitation to the surgical resection of these tumours. The gain of

knowledge regarding function, biology, and pathophysiology of the brain has resulted in the advent of advanced technology to the neurosurgeon, allowing maximal resection with minimal operative morbidity. We have reviewed the current literature concerning intraoperative imaging, fluorescence-guided resection, and awake craniotomy to generate a comprehensive overview of the

most recent developments in this field. In addition, we have provided data from our own institution confirming the beneficial effects of this multimodal approach. **Eur Assoc NeuroOncol Mag 2013; 3 (1): 11–4.**

Key words: resection, glioma, technology, MRI, awake craniotomy

■ Therapy of Malignant Gliomas – A Formidable Challenge

Gliomas of astrocytic, oligodendroglial, and ependymal differentiation comprise with an incidence of 6/100,000/year about 70 % of all intrinsic brain tumours [1]. The WHO classification system distinguishes 4 grades of malignancy [2] characterized by morphologic features such as mitotic activity, microvascular proliferation, and intratumoural necroses. The most frequent glioma of the adulthood, the glioblastoma multiforme, is a highly malignant neoplasm which displays an exceptionally poor prognosis with a median survival time of 15 months [3]. Two years after diagnosis, only 8.2 % of all patients are still alive [4]. The management of glioblastoma consists of 3 main elements: (1) microsurgical resection is followed by (2) concomitant treatment with radiotherapy plus (3) temozolomide chemotherapy [5]. In this context, the extent of surgical resection (EOR) has increasingly been recognized as an important prognostic factor in this patient population [6]. A prospective, randomized multicentre trial in glioblastoma patients has demonstrated that complete resection of the contrast-enhancing tumour leads to an overall survival of 16.7 months compared to 11.8 months after subtotal resection [7]. However, there are 2 major limitations to radical surgical resection: (1) glioblastomas display a highly infiltrative growth pattern [8] which renders complete resection virtually impossible. Careful histological studies revealed a tumour cell spread into the contralateral hemisphere in about 30 % of all patients at the time of diagnosis [9, 10]. Thus, even the most radical surgical approach will not lead to curative treatment [11]. (2) The functional anatomy of the brain consists of cortical and subcortical structures such as the primary motor cortex, Wernicke and Broca speech centres, or the internal capsule, which need to be preserved during surgical resection to avoid serious postoperative neurological deficits. Since pa-

tients with permanent neurological deficits have a significantly worse survival prognosis [12], the avoidance of any damage to these eloquent structures is mandatory in the surgical treatment of glioblastoma [13].

■ Preoperative Work-Up

Traditionally, surgery planning was conducted utilizing anatomical landmarks [14]. In the past, the identification of eloquent areas was performed in a generalized, rigid fashion based on the functional studies by Wilder Penfield, frequently leading to an inadequate assessment of the surgical risk in the individual patient [15]. The major reason for this inaccuracy is the significant individual variability of cortical organization [16]. In addition, recent studies have demonstrated a high degree of functional plasticity of the brain, which causes a significant shift of eloquent areas to distant sites especially under the condition of intracerebral tumour growth [17]. Preoperative application of functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) allows the detection of eloquent cortical and subcortical structures with high sensitivity and specificity [18, 19]. With the advent of computer-based analysis tools allowing the fusion of patho-anatomical, functional, and metabolic imaging data, it is now possible to plan and execute a precise and safe resection trajectory, thus achieving maximal EOR with minimal surgical morbidity (Figure 1). In the case of a large, infiltrative tumour, which needs to be biopsied in order to establish a histological diagnosis, it is of paramount importance to target the area of the lesion with the suspected highest grade of malignancy. In a study conducted in 81 patients who received stereotactic biopsy followed by resection of the tumour within 60 days, the biopsy-based diagnosis was incorrect in 38 %, emphasizing the limitations of stereotactic biopsy as a diagnostic tool [20]. The application of Positron Emission Tomography (PET) scanning utilizing tracers such as [¹⁸F]fluoroethyltyrosine allows to detect metabolically active areas within a larger tumour mass. The integration of these molecular imaging data into the target planning process can significantly increase the diagnostic yield of stereotactic biopsies in patients with diffuse gliomas [21, 22]. In addition, the differentiation between tumour progress and radiation-induced necrosis or pseudoprogression can be facilitated by PET scanning, supporting adequate clinical management and avoidance of unnecessary treatment measures

Received on September 25, 2012; accepted on September 30, 2012; Pre-Publishing Online on October 22, 2012

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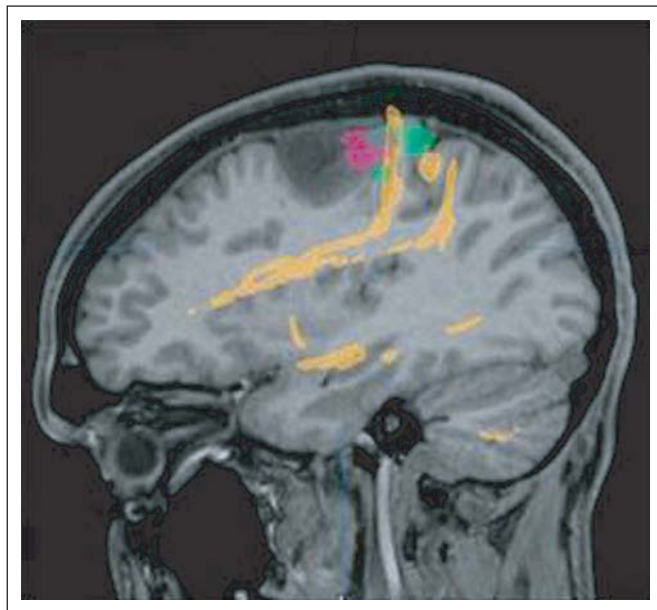


Figure 1. Fusion of [^{18} F]fluoroethyltyrosine: PET (red), functional MRI (green), and DTI tractography (yellow) in a patient with a left frontal anaplastic astrocytoma. Note the close vicinity of eloquent cortical and subcortical structures to the tumour borders.

such as repeated surgical resection [23]. Finally, detailed neuropsychological evaluation is helpful in unmasking subclinical tumour-related impairments to improve the prognostication of the postoperative course of the disease [24].

■ Intraoperative Technique

One of the most substantial obstacles to an extensive resection of gliomas is the infiltrative growth pattern of these tumours. The development of 5-aminolevulinic acid (5-ALA) as a tumour-specific fluorescence marker has caused a breakthrough in the resection of malignant gliomas [25]. The substance leads to an intracellular accumulation of fluorescent porphyrins which can be detected intraoperatively using a microscope equipped with a violet-blue excitation light source (Figure 2). A prospective, randomized controlled multicentre trial has demonstrated a significantly better EOR in the 5-ALA group compared to the control arm resected with conventional light [26]. The intraoperative localization of the tumour in addition to the adjacent, eloquent areas of the brain is greatly facilitated by the use of neuronavigation, which has also been termed frameless stereotaxy [27]. This technique is based on MRI imaging conducted with fiducial markers placed on particular landmarks of the patient's skull. Prior to craniotomy, an LED-emitting detection system linked to a computer containing the imaging data set is used to calibrate the surgical instrument set, which then allows the visualization of the resection process intraoperatively. This approach has significantly improved the safety and extent of resection in glioma patients [28, 29]. However, the accuracy of neuronavigation-based resection, which is solely based on preoperative imaging, decreases during the course of the procedure due to "brain shift" caused by the release of cerebrospinal fluid, brain swelling, and surgical manoeuvres [30]. To account for this aspect, real-time intraoperative imaging is required. Consequently, intraoperative MRI (iMRI) has been

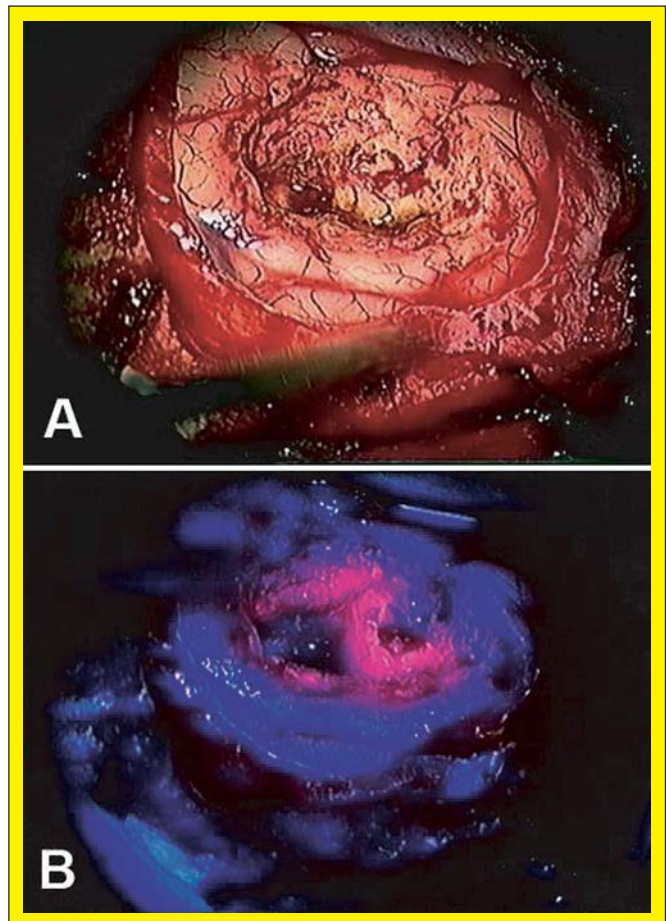


Figure 2. Resection cavity in a patient with glioblastoma following 5-aminolevulinic acid application as a fluorescence marker. (A) Under conventional light, inconspicuous adjacent white matter is visible. (B) Fluorescence illumination reveals a high-intensity signal indicating a residual tumour. Reprinted from [Stummer W, Novotny A, Stepp H, et al. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. *J Neurosurg* 2000; 93: 1003–13] with permission from the American Association of Neurological Surgeons.

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developed as an advanced technique for imaging-based resection control in glioma surgery [31]. A recent, controlled, prospective clinical trial has demonstrated that the use of iMRI leads to a better extent of resection and improved 6-month survival rates in the iMRI group compared to the control population. Interestingly, the occurrence of postoperative neurological deficits was not significantly different between the 2 study groups [32]. However, iMRI is complex, requiring either transport of the patient to the scanner during the operation or a completely antimagnetic setting in the operating room. Surgery time is prolonged due to the scanning procedure and iMRI systems are expensive and not available in the majority of neurosurgical centres [33, 34]. A valid alternative is the use of intraoperative ultrasound (IOUS), which allows real-time detection of infiltrative tumour margins [35]. However, IOUS-based resection control, albeit possible, is influenced by surgery-related artefacts and depends significantly on the experience of the surgeon [36]. As an alternative to image-based surgery, awake craniotomy with intraoperative cortical and subcortical stimulation has been established as "gold standard" to achieve maximal EOR with minimal morbidity [37]. The procedure involves tumour resection in the awake patient, allowing serial neurocognitive tests concerning motor or language function combined with direct electri-

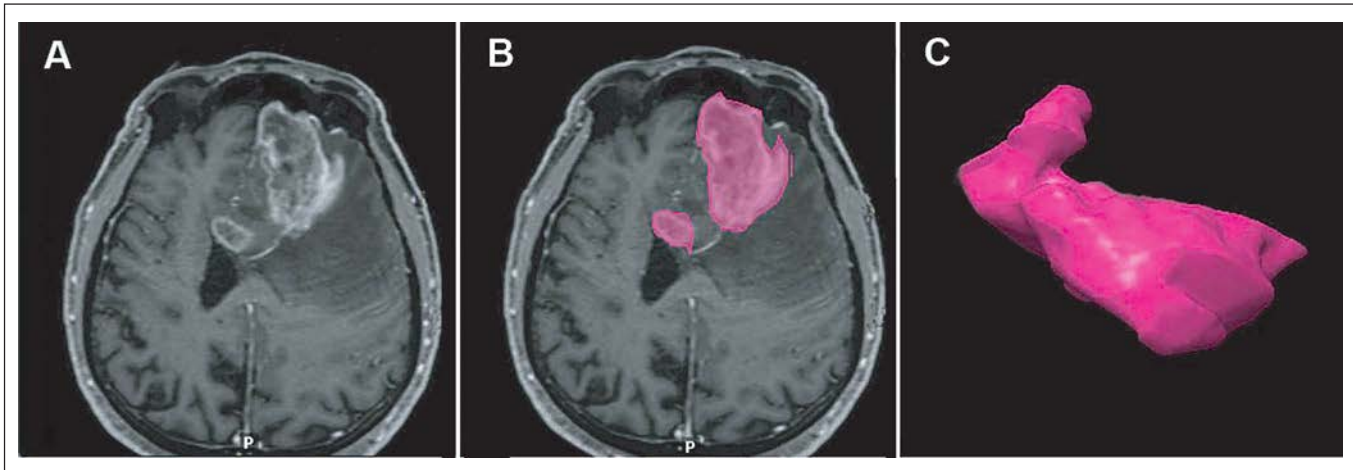


Figure 3. Quantification of the preoperative tumour volume in malignant gliomas. (A) Axial T1-weighted MRI scan of a patient with a left frontal glioblastoma. (B) The contrast-enhancing part of each section is outlined and subsequently fused to generate (C) a 3-dimensional segment which can be quantified volumetrically.

cal stimulation of the brain to unmask eloquent cortical and subcortical structures. Using this approach, a better EOR can be achieved while avoiding damage to functionally relevant brain structures [38, 39]. In order to avoid stress for the patient and to gain the best surgical results, a team of highly trained and experienced physicians consisting of anaesthesiologists, neuropsychologists, and neurosurgeons is mandatory [40]. In addition, especially if awake craniotomy is not an option, intraoperatively evoked potential monitoring is highly useful to detect damage to eloquent structures early during the procedure, allowing to correct the surgical trajectory in a timely fashion [41].

■ Results from a Single Centre – High-Tech Surgery, Is It Worthwhile?

Although it is self-evident to embrace the concept of high-tech surgery, limited resources in today's medical practice may prompt the question of whether this multimodal approach is of any clinical benefit to glioma patients. Employing the entire armamentarium outlined in this review except for iMRI, we volumetrically analyzed the EOR and clinical outcome in 44 patients with malignant gliomas (5 anaplastic astrocytoma, 39 glioblastoma) receiving surgical resection at our department. Mean age was 62.5 years, 61.4 % of all patients presenting with focal neurological deficits. Preoperative tumour size and EOR were quantified volumetrically based on MRI imaging (Iplan Cranio, Brainlab, Feldkirchen, Germany; Figure 3). In addition, surgical morbidity and mortality as well as the improvement of neurological performance were registered. There was no perioperative mortality, surgical morbidity was recorded in 9 % of all cases, caused by wound infection and CSF fistula, respectively. Complete resection (ie, no residual contrast enhancement in the postoperative scan) was achieved in 62 % of all cases, in 93 % of the patients an EOR > 90 % was accomplished. Of all patients presenting with neurological impairment, 52 % showed significant improvement. Only one patient developed transient double vision postoperatively, which completely dissipated after one week. These data confirm that the employment of advanced pre- and intraoperative technologies allows a safe and extensive resection in malignant glioma patients with a low rate of surgical morbidity.

■ Conclusion

Basic science research efforts during the decade of the brain has created an enormous gain of knowledge regarding function, biology, and pathophysiology of the brain [42]. This has caused a shift of paradigm in clinical neurosciences, including the surgical treatment of malignant gliomas. The advent of modern technology has revolutionized the preoperative work-up, surgical trajectory planning, and intraoperative monitoring with significant benefits for the patients regarding neuro-functional improvement and overall survival. In the treatment of malignant glioma, combined efforts of all involved medical specialties are mandatory to achieve the best results for the individual patient [43, 44]. Modern neurosurgery can contribute to this treatment structure by providing maximal EOR combined with minimal morbidity.

■ Conflict of Interest

The authors report no conflict of interest.

■ Funding

The study was not funded by any source.

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Emerging Immune Therapeutics Targeting Glioblastoma-Mediated Immune Suppression: Dark Before the Dawn

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Abstract: As the most common and particularly devastating primary brain malignancy, glioblastoma exerts profound immunosuppression on the anti-tumour weapons of the immune system, which also poses a tremendous obstacle to immunotherapy. By targeting glioblastoma-mediated immune suppression, enthusiasm and

confidence are accumulating based not only on the encouraging results of current clinical trials but also largely on promising preclinical findings. In this article, we summarize causes of glioblastoma-mediated immune suppression, review the current and potential approaches against several key immunosuppressive regula-

tors, and discuss the challenges and future of immunotherapy in glioblastoma treatment. **Eur Assoc NeuroOncol Mag 2013; 3 (1): 15–22.**

Key words: glioblastoma, immunosuppression, immunotherapy, clinical trials

■ Immunosuppression and Its Influence on Glioblastoma Treatment

Despite the marked advances in basic scientific research and clinical practice over the last several decades, improvements in progression-free survival (PFS) and overall survival (OS) have been modest in patients with glioblastoma – the most common and particularly devastating primary brain malignancy [1–4]. The failures of conventional glioblastoma treatments are attributed to the complex and heterogeneous tumour composition, aggressive diffuse infiltration, exuberant angiogenesis, and the tumour's capacity to escape therapies [5, 6]. Glioblastomas express a variety of tumour-associated and tumour-specific antigens such as interleukin- (IL-) 13RA, EGFRvIII, EphA2, survivin, and CMV, etc. By inducing anti-tumour immune responses, glioblastoma immunotherapy provides an alternative treatment strategy, with the theoretical advantage of tumour specificity.

Considering the presence of the blood-brain barrier, lack of lymphatic drainage, and the paucity of resident specialized antigen-presenting cells (APC) within the central nervous system (CNS), “immunological privilege” was once believed to be an inherent property of the brain. This concept has been significantly revised by the evidence of dynamic immune responses found in various physiological and pathophysiological circumstances inside the CNS [7]. In the context of glioblastoma immune responses, although there can be significant immune cell infiltration (including microglia/macrophages, lymphocytes, and dendritic cells), the anti-tumour immune responses are markedly impaired and can actually be tumour-promoting [8]. In fact, the immune responses within the glioblastoma microenvironment can be profoundly immunosuppressive and include recruitment and induction of regulatory T cells (Tregs) [9–11]; expression of immune checkpoints

(such as B7.H1/PD-L1) [12–14] and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [15]; down-regulation or absence of tumour-specific antigens; immunosuppressive cytokine secretion, such as transforming growth factor- (TGF-) β , IL-10, and vascular endothelial growth factor (VEGF) [16, 17]; and recruitment and skewing of tumour-supportive macrophages (M2 vs M1) [18, 19].

Immune therapeutic strategies that induce immune effector responses have demonstrated marked increases in PFS and OS in phase-II clinical trials of glioblastoma patients [20–25]. However, several of these trials have included in the enrolment criterion a requirement for gross-total resection in order to minimize glioblastoma-mediated immune suppression. Unfortunately, not all glioblastoma patients are subjected to extensive resections or may have medical contraindications. If glioblastoma-mediated immune suppression could be controlled, then theoretically, immune recognition and clearance should occur.

■ Current Clinical Trials Targeting Glioblastoma-Mediated Immunosuppression

Numerous glioblastoma immunotherapeutic clinical trials are underway, with most designed to prime/amplify the host anti-tumour immune responses rather than to abrogate or reverse glioblastoma-mediated immunosuppression. According to the ClinicalTrials.gov database (<http://www.clinicaltrials.gov/>, updated to November 2012), there are less than 10 completed or active glioblastoma immunosuppression-targeted clinical trials documented among more than 120 clinical trials related to glioblastoma immunotherapeutics. Among the limited glioblastoma immunosuppression-targeted clinical trials, most are phase-I studies evaluating the pharmacokinetic and toxicological properties of certain reagents, or exploratory studies determining the correlation between immune status modulation and drug intervention (Table 1).

TGF- β Pathway

Transforming growth factor β 2 (TGF- β 2) is a potent cytokine with multiple biological activities [26] that has been found to

Received on December 10, 2012; accepted on December 21, 2012

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Table 1. Clinical and preclinical trial targets and results for glioblastoma-mediated immunosuppression. The Cancer Genome Atlas glioblastoma database of mRNA data (Agilent microarray, sample number: 500, updated to 11/30/2012) was used as the source of data for expression and survival evaluation, and data were analyzed through the open access cBio Cancer Genomics Portal at www.cbioportal.org. The glioblastoma tissue analyzed contains glioma cells as well as tumour-supportive stromal and infiltrating immune cells. To define the expression alternation of certain mRNAs, the z-score threshold (the number of standard deviations above the mean expression level of the selected gene) was set to ± 1 . The up-regulated (up) and down-regulated (down) percentages of the mRNAs within all available glioblastoma samples and their respective correlations with overall survival (OS)/disease-free survival (DFS) are listed.

Targets	Classification	mRNA alternation within GBM	Overall survival correlation	Disease free survival correlation	Therapeutic strategy	Therapeutic agents	ClinicalTrial.gov access #	Phase	Results
TGF- β	Immunosuppressive cytokine	Up: 11.2 % Down: 16.0 %	Up: ns Down: positive ($p = 0.027$)	Up: ns Down: positive ($p = 0.012$)	Anti-sense oligonucleotide; antibody blockade	Trabedersen (AP 12009) GC1008	NCT00431561 NCT00761280 NCT01472731	II/III/II	Survival benefit for a sub-group of GBM patients (phase II)
TGFBR1	Immunosuppressive cytokine receptor	Up: 7.8 % Down: 13.0 %	Up: ns Down: ns	Up: ns Down: ns	Small molecule inhibitor	LY2157299	NCT01220271	I/II	–
IL-2R α (CD25)	Treg marker	Up: 25.0 % Down: 11.6 %	Up: ns Down: ns	Up: negative ($p = 0.0048$) Down: ns	Antibody blockade	Basiliximab Daclizumab	NCT00626015 NCT00626483	I/II	Well-tolerated; peripheral Treg reduction
VEGF-A	Immunosuppressive cytokine	Up: 15.6 % Down: 20.6 %	Up: ns Down: ns	Up: negative ($p = 0.016$) Down: ns	Antibody blockade	Bevacizumab	NCT01091792	0	–
CTLA-4	Immune checkpoint	Up: 12.2 % Down: 12.0 %	Up: ns Down: ns	Up: ns Down: ns	Antibody blockade	Ipilimumab Tremelimumab	–	–	–
PD-1	Immune checkpoint	Up: 8.4 % Down: 12.4 %	Up: ns Down: ns	Up: ns Down: ns	Antibody blockade	MDX-1106	–	–	–
PD-L1	Immune checkpoint	Up: 8.8 % Down: 18.0 %	Up: ns Down: positive ($p = 0.044$)	Up: negative ($p = 0.063$) Down: positive	Antibody blockade	MDX1105-01	–	–	–
STAT3	Transcription regulator	Up: 13.0 % Down: 17.0 %	Up: negative ($p = 0.0095$) Down: ns	Up: negative ($p = 0.042$) Down: ns	Small molecule inhibitor	WP1066	–	–	–
IDO	Immunosuppressive enzyme	Up: 9.8 % Down: 1.6 %	Up: ns Down: ns	Up: ns Down: ns	Small molecule inhibitor	1-MT	–	–	–
Arg-1	Immunosuppressive enzyme	Up: 14.0 % Down: 17.8 %	Up: ns Down: ns	Up: ns Down: ns	Small molecule inhibitor	no-NOHA	–	–	–
ns: non-significant; positive: the OS/DFS of an altered gene set is larger than for unaltered ones, $p < 0.05$; negative: the OS/DFS of an altered gene set is smaller than for unaltered ones, $p < 0.05$.									

be over-expressed in more than 90 % of high-grade gliomas [27–29], making it an attractive target for glioblastoma treatment. Inhibition of TGF- β 2 in tumour tissue leads to reversal of tumour-induced immune suppression as well as inhibition of tumour growth, invasion, and metastasis [30, 31]. Trabedersen (AP 12009) is a synthetic antisense phosphorothioate oligodeoxynucleotide complementary to the human TGF- β 2 mRNA, whose safety and efficacy has been shown through various pharmacokinetic and toxicology studies, both in vitro and in vivo, as well as in phase-I/-II dose-escalation studies [32–34]. The overall outcome was negative for the pre-specified primary endpoint in the randomized phase-IIb study comparing a dose of either 10 μ M or 80 μ M of trabedersen with standard chemotherapy in a cohort of 145 patients with recurrent or refractory anaplastic astrocytoma or glioblastoma (Trial Registration: ClinicalTrials.gov NCT00431561). Nevertheless, survival at 2 and 3 years for glioblastoma patients in a small subgroup (≤ 55 years old, with an initial Karnofsky Performance scale score of > 80) who received 10 μ M trabedersen was 3-fold higher than for those receiving chemotherapy [35]. Despite the controversy over the interpretation of the clinical trial data [36, 37], a multinational phase-III study entitled SAPPPIRE was underway investigating the efficacy and safety of 10 μ M trabedersen compared with standard chemotherapy in adult patients with confirmed recurrent or refractory anaplastic astrocytoma or secondary glioblastoma, but it was terminated due to slow patient recruitment (Trial Registration: ClinicalTrials.gov NCT00761280).

In addition to trabedersen, several other drugs targeting the TGF- β pathway are now being tested in phase-I/II clinical trials. For instance, GC1008 is an antibody capable of neutralizing TGF- β , and a phase-II clinical trial is open to determine its safety, tolerability, pharmacokinetics, and pharmacodynamics in primary malignant glioma patients (Trial Registration: ClinicalTrials.gov NCT01472731). LY2157299 is another new small molecule drug antagonizing the TGF-

β receptor I/II kinase [38] that is being tested in a phase-I/II clinical trial with temozolomide-based radiochemotherapy in patients with newly diagnosed malignant glioma (Trial Registration: ClinicalTrials.gov NCT01220271).

CD25/IL-2R α

An increase in the Treg fraction and amount of Treg infiltration has been verified as an immunosuppression-related characteristic in the peripheral blood and tumour tissue of glioma patients, especially in high-grade gliomas [9–11]. Expression of alpha chain of the IL-2 receptor (CD25/IL-2R α) not only serves as a Treg phenotypic marker, but it also empowers the Treg to induce IL-2 cytokine deprivation-mediated apoptosis of effector T cells [39, 40]. Preclinical studies conducted by Dr John Sampson's group have shown that systemic Treg cell depletion with anti-mouse CD25 mAb (Clone PC61) can significantly extend survival in an SMA-560 glioma syngeneic mouse model system [41]. Inspired by this, several anti-CD25-based phase-I/II clinical trials in glioblastoma patients have been initiated with basiliximab (Trial Registration: ClinicalTrials.gov NCT00626015) and daclizumab (Trial Registration: ClinicalTrials.gov NCT00626483). Both basiliximab and daclizumab are mouse-human chimeric monoclonal antibodies that specifically block IL-2-to-IL-2R α binding and were initially designed and approved by the US Food and Drug Administration (FDA) to prevent acute rejection after organ transplantation. In contrast to the PC61 antibody which depletes murine CD25⁺ T cells, basiliximab and daclizumab act through a non-depleting mechanism [42]. The purpose of the current clinical trials is to study the safety and combinatorial approaches for patients with resected glioblastoma. Previous attempts to selectively eliminate Tregs with denileukin diftotox (ONTAK, a fusion protein of diphtheria toxin and IL-2) and LMB-2 (a fusion protein of an anti-IL-2R α monoclonal antibody and exotoxin) resulted in mixed success and off-target limitations [43]. Of note, a recently published randomized placebo-controlled pilot study indicates that daclizumab treatment is well-tolerated with no symptoms of autoimmune toxicity and resulted in a significant reduction in the frequency of circulating CD4⁺FoxP3⁺ Tregs cells relative to saline controls [44], indicating that further large-scale studies are warranted.

VEGF

Dynamic endothelial cell proliferation and abnormal vessel formation are among the major characteristics of glioma pathology, which are mainly driven by elevated VEGF signalling in the tumour microenvironment [45, 46]. Via ligand interaction with VEGFR, VEGF initiates PI3K/Akt, MEK/Erk, and other signalling pathways, which trigger endothelial cell adhesion, migration, and growth [41]. Along with its proangiogenesis effect, VEGF induces immunosuppression and other regulatory functions to promote glioma progression [48, 49]. The anti-VEGF monoclonal antibody bevacizumab has been approved by the FDA for the treatment of glioblastoma since 2009. Although there is still considerable debate regarding the overall survival benefit of bevacizumab and whether or not it induces more infiltrative glioma recurrence in some patients [50], it has been shown to prolong PFS and control peritumoural oedema [51]. A phase-0 clinical trial has been opened for newly diagnosed glioblastoma patients to evaluate

the respective roles of radiotherapy, temozolomide (TMZ), and bevacizumab on Treg shift and modulation of the immune system (Trial Registration: ClinicalTrials.gov NCT01091792).

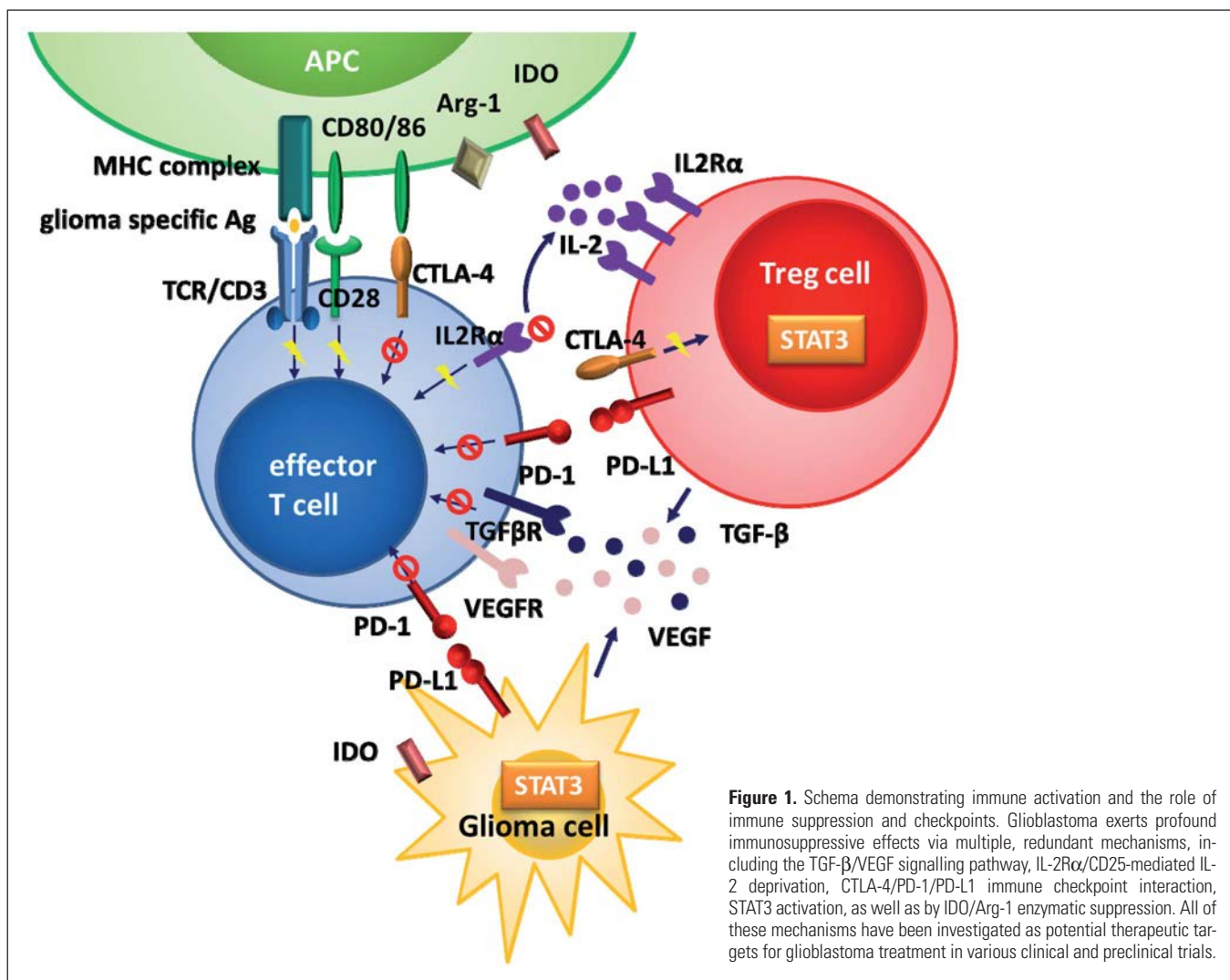
Several studies have suggested that bevacizumab may improve immunological responses by abrogating VEGF-induced inhibition on dendritic cells, reconstitution of the lymphocyte compartment, modulation of cytokine secretion, and decreasing the Treg fraction [52–55]. Consequently, a phase-II clinical trial of EGFRvIII peptide in combination with bevacizumab (Trial Registration: ClinicalTrials.gov NCT00671970) has been initiated. However, human glioblastoma tumours and their murine xenografts have been shown to have markedly increased expression of immune suppressive signal transducer and activator of transcription 3 (STAT3) upon failing to respond to bevacizumab therapy [56], suggesting that sustained use of bevacizumab may hinder immune therapeutic approaches. To date, no published studies have evaluated the synergistic activity of bevacizumab and immunotherapy in murine glioma model systems.

■ Proposed Therapeutics Targeting Glioblastoma-Mediated Immunosuppression

Unfortunately, most present clinical trials abrogating glioblastoma-mediated immune suppression suffer from small sample size, administration optimization, and bias induced by patient selection. It is too early to draw conclusions regarding therapeutic success or failure of these approaches based on these limited clinical trials. However, the observations of clinical symptom alleviation, survival advantage in select patients, low toxicity, and supplementary effect to standard treatments have generated enthusiasm. Moreover, with the identification of key hubs in glioblastoma-mediated immunosuppression, preclinical findings have indicated broad and encouraging opportunities to enhance anti-tumour immunity. Some of these targets have been well-tested in other types of cancer. Given extensive preclinical data and target expression analysis, we are clearly on the precipice of evaluating therapeutic efficacy of several approaches targeting glioblastoma-mediated immune suppression.

CTLA-4

T-cell activation is initiated through antigens presented in the context of the major histocompatibility complex (MHC) to the T-cell receptor (TCR; Figure 1). The T-cell response status and amplitude are regulated by the balance between co-stimulatory and inhibitory signals [57, 58]. Specifically, CD28 signalling by binding to co-stimulatory molecules such as CD80 (B7.1) and CD86 (B7.2) provides the second signal for T-cell proliferation, resulting in pro-inflammatory cytokine secretion and cytotoxic killing. On the contrary, inhibitory signals, or so-called immune checkpoints, down-regulate the activation signal and induce T-cell inactivation, anergy, and apoptosis to maintain immune homeostasis. In the case of glioblastoma, these immune checkpoint haemostatic mechanisms can be up-regulated inappropriately by the tumour to limit immune recognition and elimination of the malignancy [13, 14, 59]. Well-characterized checkpoint molecules that play a role in tumour immune suppression include the cyto-



toxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1) [60, 61].

CTLA-4 is expressed on T cells and exhibits a higher affinity for CD80/CD86 than the co-stimulatory receptor CD28 [62–64]. Although the exact suppressive mechanism of CTLA-4 is still uncertain, it is proposed that CTLA-4 counteracts CD28 activity by both competitively inhibiting CD80/CD86 binding and actively transmitting inhibitory signals [65, 66]. Moreover, CTLA-4 knockout or blockade significantly inhibits the ability of Tregs to regulate both autoimmunity and antitumour immunity [67, 68], which indicates that CTLA-4 can also enhance Treg function to indirectly induce effector T-cell inhibition.

An anti-human CTLA-4 antibody, ipilimumab, has recently been approved by the FDA for the treatment of stage-IV melanoma [69], which begets enthusiasm for CTLA-4 blockade in the treatment of other cancers. Furthermore, radiographic responses have been observed in melanoma patients with CNS metastasis treated with ipilimumab. In preclinical studies with the murine SMA-560 intracranial glioma model, systemic administration of anti-CTLA-4 Ab (Clone 9H10) conferred long-term survival in 80 % of treated mice, without eliciting experimental allergic encephalomyelitis. CTLA-4 blockade re-established a normal CD4 fraction, restored T-

cell proliferation, and abrogated dysregulated Tregs [15]. Recently, Fong et al revealed that dynamic expression of CTLA-4 on peripheral blood CD4⁺ and CD8⁺ T lymphocytes was significantly associated with survival of glioblastoma patients receiving dendritic cell vaccination [59], which further supports enthusiasm for targeting CTLA-4 in glioblastoma patients. Thus, a phase-II/III randomized, double-blinded placebo-controlled clinical trial (RTOG 1125) was devised to compare PFS and OS between newly diagnosed glioblastoma patients receiving standard-of-care adjuvant temozolomide to those treated with adjuvant temozolomide and ipilimumab; however, the study was cancelled when financial support by the sponsor was withdrawn.

PD-1

Programmed cell death protein 1 (PD-1) is another immune checkpoint receptor expressed by activated T cells. While CTLA-4 regulates T cells at the initial stages of activation, PD-1 dampens the immune response during later stages of T-cell activation by interacting with its ligands, programmed cell death protein 1 ligand 1 (PD-L1/B7-H1) and PD-L2 (B7-DC), expressed on hematopoietic cells, including antigen-presenting cells (APCs), T cells, B cells, macrophages, and stromal cells [70–73]. Its ligand PD-L1 is also expressed by glioblastoma cells, including the cancer stem cells [12–14, 74], indicating this PD-1/PD-L1 pathway is a relevant thera-

peutic target for glioblastoma patients. In addition, PD-1 participates in the regulation of humoral immunity [75, 76] and innate immunity [77], suggesting that this mechanism might exert an even broader regulatory effect on immune responses than CTLA-4. Of note, PD-1 is highly expressed on Tregs and enhances Treg proliferation [78].

Inspiringly, the results from 2 phase-I clinical trials (Trial Registration: ClinicalTrials.gov NCT00730639 and NCT00729664) using monoclonal antibodies that antagonize the PD-1/PD-L1 pathway (MDX-1106 for PD-1 and MDX1105-01 for PD-L1) were reported recently for several tumour types, including advanced melanoma, non-small-cell lung, prostate, renal, colorectal, ovarian, pancreatic, gastric, and breast cancers. Antibody-mediated blockade of the PD-1/PD-L1 pathway induced durable tumour regression (objective response rate of 6–28 %) without severe toxicity (grade-3 or -4 drug-related adverse event rate of 9–14 %) [79, 80]. Based on these encouraging results, the strategy of blocking the PD-1/PD-L1 pathway might provide a new benchmark for anti-cancer immunotherapy [81, 82]. Given the PD-L1 expression on glioma cells, the established role of the PD-1/PD-L1 pathway in glioma immunosuppression, and the relationship between PD-L1 expression on tumour cells and the anti-PD-1 therapy objective response [80], a clinical trial of these agents in glioblastoma patients, including stratification based on expression, warrants consideration. Preclinical studies have demonstrated prolonged survival in the intracranial GL261 glioma C57/BL6 murine model using the combination of anti-PD-1 therapy and radiation therapy when compared with either modality alone [83].

STAT3

STAT3 is a key transcription factor that drives the fundamental components of malignancy and invasion (including in gliomas) and is considered a master transcriptional regulator of tumorigenesis [84]. Although not mutated in glioma, STAT3 is phosphorylated and therefore activated in nearly all gliomas. Many growth factors and cytokines, including IL-6 that is expressed in the CNS, activate Jak2, which subsequently activates STAT3 by phosphorylation of the tyrosine residue in the transactivation domain. Phosphorylated STAT3 (p-STAT3) then translocates into the nucleus and induces a variety of effector molecules. STAT3 is frequently over-expressed in tumour cells, including gliomas [85], and drives tumorigenesis by preventing apoptosis (by increasing survivin, Bcl-xl, and Mcl-1 expression) and enhancing proliferation (by increasing c-Myc and cyclin D1/D2 expression), angiogenesis (by increasing VEGF and hypoxia-inducible factor- [HIF-] 1 α expression), and invasiveness (by increasing matrix metalloproteinase- [MMP-] 2/9 expression) [86, 87] – including specifically within gliomas [19, 88–90].

STAT3 has also been strongly implicated as a key regulator of immunosuppression in patients with cancer [91]. The p-STAT3 pathway is activated in the immune cells, especially the immune cells that reside within the tumour microenvironment [92], which down-regulates the anti-tumour immune responses of the immune cells. Others have shown that the up-regulation of p-STAT3 reduces the expression of MHC II, CD80, CD86, and IL-12 in dendritic cells, rendering them unable to stimulate T cells and generate effective anti-tumour

immunity [92] and that STAT3 is a transcriptional regulator of FoxP3 expression in Tregs [93]. We have shown that human glioblastoma can specifically polarize macrophages via the STAT3 pathway toward an immunosuppressive and tumour-supportive M2 phenotype [19] that then contributes to angiogenesis and tumour invasion and is a negative prognosticator for long-term survival in genetically engineered murine model systems of glioma [18].

Recent studies have indicated that STAT3 is essential for glioma cancer stem cell (gCSC) maintenance [94, 95]. gCSCs have the capacity for self-renewal, and their main feature is their ability to initiate a tumour in mice. gCSCs have been shown to recapitulate the characteristics of glioblastoma [96], and they are also believed to confer the resistance to chemotherapy and radiation observed in glioblastoma [97, 98]. They are also profoundly immune suppressive and can express CTLA-4 and B7-H1 [99]. Moreover, gCSCs elaborate a variety of immune suppressive cytokines such as galectin-3 and TGF- β that inhibit T-cell proliferation and activation, induce FoxP3⁺ Tregs, trigger T-cell apoptosis, and induce macrophages/microglia to become polarized to the tumour-supportive p-STAT3-expressing M2 phenotype [19, 100]. Many think that without targeting the gCSC population of cells therapeutically, malignant gliomas will continue to persist and recur.

WP1066 blocks the nuclear translocation of p-STAT3 into the nucleus [101, 102] and achieves excellent penetration into the CNS. Therapeutic efficacy with WP1066 has been demonstrated against head and neck carcinoma [103], pancreatic cancer [104, 105], bladder cancer [106], B-cell non-Hodgkin's lymphoma and myeloma [107], and chronic myelogenous leukaemia [108]. WP1066 has demonstrated therapeutic efficacy against metastatic [109] and established CNS melanoma in murine models [110]. The therapeutic effects of WP1066 can be partially ablated with in vivo depletions of the CD4⁺ and CD8⁺ population or by implanting B16 melanoma or GL261 glioma in nude mouse model systems, indicating that part of the therapeutic effect of WP1066 is immunologically mediated [110]. WP1066 has demonstrated therapeutic efficacy against subcutaneously implanted U-87 MG cells [89] and in 2 distinct Ntv-A murine models of gliomas, those induced by RCAS-PDGFB + RCAS-bcl-2 [89] and by RCAS-PDGFB + RCAS-STAT3 [88].

We have also demonstrated that STAT3 blockade with WP1066 can significantly modulate tumour-mediated immune suppression. Specifically, WP1066 can induce the expression of co-stimulatory molecules on peripheral macrophages and tumour-infiltrating microglia ex vivo from glioblastoma patients. WP1066 treatment of the peripheral blood from glioblastoma patients who are immunologically anergic resulted in marked production of pro-inflammatory cytokines including IL-2, IL-4, IL-12, and IL-15. STAT3 blockade with WP1066 was sufficiently potent to induce proliferation of effector T cells from glioblastoma patients who were refractory to CD3 stimulation, and mechanistically, this was found to be secondary to the activation of ZAP-70 in the T cells and inhibition of Tregs [111]. Furthermore, the immunosuppressive properties of GSCs were markedly diminished when the GSCs were treated with either siRNA targeting STAT3 or with WP1066

[19, 100]. Specifically, the gCSC-mediated effects of inhibiting T-cell proliferation and inducing Tregs were markedly diminished when the STAT3 pathway was blocked in the gCSCs. Furthermore, WP1066 could inhibit the gCSC-conditioned medium polarization of the macrophage/microglia to the M2 immune suppressive, tumour-propagative phenotype, and inhibited the secretion of the immunosuppressive cytokines interleukin-10 (IL-10) and TGF- β 1 by the M2 macrophages/microglia. Combined, these data indicate that WP1066 can reverse both innate and adaptive tumour-mediated immune suppression. Cumulatively, these data provide compelling rationale for therapeutically targeting the STAT3 pathway. It is anticipated that WP1066 will be entering clinical trials for glioblastoma patients within the next year.

Indoleamine 2,3-Dioxygenase

Indoleamine 2,3-dioxygenase-1 (IDO) is an inducible enzyme that converts tryptophan to kynurenine. It has been demonstrated to be a potent immunosuppressive regulator expressed by cancer cells as well as by infiltrating immune cells, including dendritic cells and myeloid-derived suppressor cells (MDSCs) [112, 113]. Up-regulated by high IFN- γ and TGF- β within the tumour microenvironment, IDO utilizes various mechanisms to induce local immunosuppression, including depletion of the essential amino acid tryptophan, tryptophan toxic metabolite accumulation, NF- κ B signalling activation that leads to effector T-cell suppression and Treg induction, up-regulation of inhibitory TGF- β and CTLA-4, and modulation of the maturation and/or function of dendritic cells [114]. In addition, IDO expression induces Treg recruitment and inhibition of T-cell-mediated glioma immunity, which suggests a critical role for IDO-mediated immunosuppression in glioblastoma [115]. Recently, Dr Maciej Lesniak's group demonstrated that IDO down-regulation in glioma predicts a better prognosis in both mouse models and human patients.

The potential of IDO as a therapeutic target in glioblastoma treatment has been investigated in several preclinical studies [116, 117]. The agent 1-methyl-tryptophan (1-MT) is a competitive inhibitor for IDO [118]. Several phase-I clinical trials based on 1-MT are underway in advanced solid tumours, including breast, lung, and pancreatic cancers as well as melanoma. Although there is no current clinical trials of IDO inhibition in glioblastoma patients, this is also a potential approach in glioblastoma treatment. Of note, selective inhibition of IDO is expected to exert a therapeutic effect without significant side effects because IDO is an inducible enzyme [119].

Arginase-1

As a marker of tumour-supporting M2 macrophages [120, 121] and MDSCs [122], arginase-1 (Arg-1) has been shown to exert immunosuppressive effects through the consumption of L-arginine, a critical cofactor for sustained T-cell activation [123, 124]. Increased Arg-1 level and activity are observed in the plasma obtained from patients with glioblastoma, suggesting the functional dysregulation of circulating neutrophils and MDSCs. Interestingly, *in vitro* T-cell suppression induced by peripheral blood mononuclear cells (PBMCs) from glioblastoma patients could be reversed by the specific Arg-1 inhibitor nor-NOHA or by arginine supplementation [125, 126].

Other Targets

Other potential targets for glioblastoma-mediated immune suppression include IL-10 [127, 128], GITR [129, 130], and inducible nitric oxide synthase (iNOS) [131]. Although there are no current clinical trials in glioblastoma patients targeting these molecules, agents targeting these are being evaluated in other types of cancers and have shown promise.

Perspectives

A fundamental challenge for targeting glioblastoma-mediated immune suppression is tumour heterogeneity. This feature undoubtedly contributes to the tumour's aggressiveness and poses a tremendous obstacle to the glioblastoma treatment, including immunotherapy [132]. With the plethora of immunosuppressive mechanisms described to date and the possibility of more yet to be identified, multiple, redundant mechanisms are utilized by glioblastoma to escape host immune attack. It would be anticipated that the targeting of one immunosuppressive mechanism would result in the rapid appropriation of alternative mechanisms. A key reason for immunotherapeutic failure is the dynamic immunoediting and immune escape within the glioma environment [133]. It is very likely that an optimized arsenal of multiple immunotherapeutics targeting corresponding mechanisms and used in combination with other standard approaches will be necessary to exert a sustained suppression of malignancy.

Alternatively, agents could be used that target networks of immune suppression. MicroRNAs (miRNAs) are a group of small non-coding RNA molecules, which post-transcriptionally regulate genes by binding to the 3'-untranslated region (UTR). Interestingly, one single miRNA can regulate multiple target genes and vice versa. Because miRNAs have been demonstrated to modulate tumour cell proliferation and apoptosis and to act as oncogenes or tumour-suppressor genes, the connection between tumour-mediated immune suppression and miRNAs has yet to be explored. Our preliminary studies have shown that miRNA dysregulation is present in the glioma microenvironment and that it participates in the glioma-mediated immunosuppression. Moreover, selective miRNA administration or inhibition can exert potent anti-glioma therapeutic effects via the immune system and can target multiple immunosuppressive mechanisms simultaneously (unpublished data, 2012). Thus, these miRNAs may represent a new class of immune therapeutics that have the potential to modulate multiple mechanisms of glioblastoma-mediated immune suppression.

Conclusions

Complex and profound glioblastoma-associated immunosuppression abrogates anticancer immune responses. The limited success of current glioblastoma immunotherapy further provokes the necessity for new approaches. Recent preclinical findings targeting the key hubs of glioblastoma-mediated immunosuppression along with lessons learned from the other cancers indicate broader and more encouraging opportunities. Despite the tremendous challenges and difficulties ahead, multiple-target or personalized glioblastoma-mediated immune suppression therapeutic targeting combined with other

standard approaches will undoubtedly bring the dawn to glioblastoma treatment.

Acknowledgments

We thank Audria Patrick and David M Wildrick, PhD, for editorial assistance. Grant support was graciously provided by The Anthony Bullock III Foundation (ABH), Cynthia and George Mitchell Foundation (ABH), the Dr Marnie Rose Foundation (ABH), and the National Institutes of Health CA120813-01, P50 CA127001 (ABH), and the China Scholarship Council (SX).

Conflict of Interest

The authors state that no conflicts of interest exist.

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Virology of Malignant Brain Tumours

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Abstract: Glioblastoma multiforme is the most common and most aggressive type of primary malignant brain tumour, accounting for 52 % of all primary brain tumour cases and 20 % of all intracranial tumours. Evidence for a viral cause of glioblastoma has been postulated, possibly SV40 or more likely cytomegalovirus (CMV). A viral cause is difficult to substantiate, since CMV infection is so common and malignant brain tu-

mours are so rare. One possible basis for a CMV-glioblastoma association may be the "hit-and-run" hypothesis. CMV might be capable, under certain conditions, of acting as a cell mutagen. Age at infection may be one of these conditions, since the incidence of both glioblastoma multiforme and CMV infection are related to socioeconomic status. CMV infection in early childhood, more common in lower socioeconomic

groups, may be protective against glioblastoma multiforme, whereas CMV infection in later childhood or adulthood may be a risk factor for glioblastoma. If so, glioblastoma occurrence would resemble paralytic polio, where low socioeconomic status, poor hygiene, and early infection are protective. **Eur Assoc NeuroOncol Mag 2013; 3 (1): 23–4.**

■ Introduction

Glioblastoma multiforme is the most common and most aggressive type of primary malignant brain tumour, accounting for 52 % of all primary brain tumour cases and 20 % of all intracranial tumours [1]. The only effective chemotherapy is temodar [2]. Glioblastoma multiforme is more common in males and appears to be sporadic, without any genetic predisposition. No links have been found between glioblastoma multiforme and smoking or diet. The relation to cell phones is still uncertain [3]. An association between malignant brain tumour and malaria may indicate anopheles mosquito transmission of an etiologic agent, possibly a virus [4].

Cytomegalovirus (CMV) may be a risk factor [5–7], though the CMV-glioblastoma association is controversial [5]. CMV does transform normal cells into cancerous cells [8, 9], and has been implicated as a risk factor in cancers of the cervix [10], prostate [11], and colon [12]. In addition, CMV sequences and viral gene expression exist in most, if not all, malignant gliomas [13].

■ Risk Factors and Cancer

A risk factor and cancer can interact in 3 ways. The first is the simplest. When a rare form of cancer is associated with a rare exposure, the link between the risk and the cancer stands out clearly. The association can often be discerned accurately by observation alone. A striking example is scrotal cancer. In 1775, a London surgeon, Sir Percivall Pott, discovered that scrotal cancer was much more common in chimney sweeps than in the general population. The link between an unusual malignancy and an uncommon profession was so striking that Pott did not even need statistics to prove the association. Pott discovered one of the first clear links between an environmental carcinogen and a particular type of cancer [14].

A more vexing situation occurs when a common exposure is associated with a common form of cancer. An example is tobacco smoking and lung cancer. In the mid-1920s, smoking was so common and lung cancer so prevalent that it was initially impossible to definitively identify a statistical link between the 2. No one knew whether the intersection of the 2 phenomena was causal or accidental, until smoking was later identified as a major cause of many cancers through careful clinical studies in the 1950s and 1960s [14].

The most complex intersection between a risk factor and cancer often occurs in the third instance, when a common exposure is associated with a rare form of cancer. This is cancer epidemiology's most difficult problem. Cell phones and brain tumours are one example. A second is the possible relationship of CMV to glioblastoma [14].

■ Problematic Cytomegalovirus Involvement

Cobbs et al reported that a high percentage of malignant gliomas are infected by CMV and multiple CMV gene products are expressed in these tumours [15]. Mitchell et al found that 80 % of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood, while seropositive normal donors and other surgical patients did not exhibit detectable virus [16]. Mitchell et al suggested an association of CMV with malignant gliomas and proposed that subclinical CMV viremia is a previously unrecognized manifestation of glioblastoma multiforme.

In our own studies, we have collected peripheral blood in anticoagulated tubes from 10 patients with newly diagnosed glioblastoma multiforme referred for radiation therapy [17]. We used standard methods for detecting CMV by reverse transcriptase-polymerase chain reaction (RT-PCR) [18] and peripheral blood culture [19]. None of our 10 patients had circulating CMV detected. Mitchell et al reported that 80 % of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood [16]. The chance of a single glioblastoma patient not having detectable cytomegalovirus would be 20 % or 0.2. Therefore, the chance of none of 10 patients having detectable cytomegalovirus would be 0.2^{10} or $p = 0.000000124$.

Received on October 27, 2012; accepted on November 13, 2012; Pre-Publishing Online on December 18, 2012

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Moreover, CMV seropositivity data and glioblastoma incidence data do not support a CMV-glioblastoma association, since CMV seroprevalence rates are not consistently related to glioblastoma incidence rates [20]. CMV seroprevalence is, however, related to socioeconomic status. CMV infection is significantly lower in whites than in blacks or Hispanics (Mexican Americans), while glioblastoma incidence is higher. CMV seroprevalence rates are significantly higher in women than men, although glioblastoma is more common in men. Therefore, a possible CMV-glioblastoma association cannot be readily substantiated with CMV seropositivity rates.

Possible Basis for CMV Involvement

One possible basis for a CMV-glioblastoma association is the “hit-and-run” hypothesis [21]. CMV might be capable, under certain conditions, of acting as a cell mutagen.

Age at infection may be one of these conditions, since the incidence of both glioblastoma multiforme and CMV infection are related to socioeconomic status, as described above. CMV infection in early childhood, more common in lower socioeconomic groups, may be protective against glioblastoma, whereas CMV infection in later childhood or adulthood may be a risk factor for glioblastoma. If so, glioblastoma occurrence would resemble paralytic polio, where low socioeconomic status, poor hygiene, and early infection are protective [22].

Conflict of Interest

None.

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Low-Grade Glioma, Refractory Epilepsy, VPA Encephalopathy, and Chemotherapy Supporting Seizure Control: A Complex Case

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Introduction

Seizures in patients with low-grade glioma are frequent and the most common leading symptom. Treatment of seizures in such patients can be challenging and sometimes a combination of several antiepileptic drugs is necessary.

We report on a patient with a long history of a low-grade glioma and seizures who developed a life-threatening complication of antiepileptic drug therapy.

Case Report

A 73-year-old male suffered from a fibrillary astrocytoma (WHO 2) of the left frontal lobe since 1989. Initial diagnosis was confirmed by biopsy. After surgery, focal radiotherapy with a dose of 60 Gy was performed. Initial focal seizures were controlled with phenytoin for a few years, but antiepileptic drug treatment had to be switched to carbamazepine and clonazepam due to seizure recurrence. In 2002, levetiracetam was added. The patient was followed up at other hospitals until July 2010, therefore seizure control could not be assessed. At this time, first radiological signs of progression of the tumour with new contrast enhancement lead to re-operation with partial resection. Post-OP histological diagnosis showed pure necrosis.

Over the next 16 months, seizure frequency increased and in February 2012, the patient was admitted to our centre due to frequent, daily focal seizures with and without impairment of consciousness. At this time, medication consisted of levetiracetam 3000 mg/d, topiramate 450 mg/d, and phenytoin 200 mg/d. Phenytoin was discontinued as it was suspected to worsen the patient's gait disturbance, which was primarily attributed to post-radiation white matter changes. Lacosamide and subsequently valproic acid were added without any effect on seizure frequency. MRI at this time showed a residual tumour with no clear signs of tumour progression. As a consequence of intractable seizures despite triple AED therapy, chemotherapy with temozolomide was recommended but not initiated due to acute deterioration of the clinical condition. Surgery was not recommended due to the risk of causing neurological deficits. Almost 2 weeks after the start of valproic acid at a dose of 1000 mg/d the patient became somnolent to stuporous with swallowing difficulties and developed aspiration pneumonia. Due to an elevated ammonium level of 69 $\mu\text{mol/l}$ (normal: 12–47 $\mu\text{mol/l}$) and continuous generalized slowing in the EEG, valproate-induced hyperammonemic encephalopathy was diagnosed. After abrupt discontinuation of

valproic acid and with antibiotic therapy the patient recovered. Triple therapy consisting of levetiracetam, topiramate, and phenytoin was again reintroduced and the seizures were well controlled until September 2012. At this time the patient experienced new seizure aggravation combined with cognitive decline. MRI now indicated tumour progression with signs of malignancy (Figure 1). Chemotherapy with temozolomide (dose-dense one week on/one week off [120–150 mg/m²]) was started and after one month seizures disappeared completely. Neurological status indicated no focal deficit, but moderate cognitive impairment, mild gait disorder, and a Karnofsky Performance Score (KPS) of 60.

Conclusions

Seizures are sometimes difficult to treat in patients with low-grade glioma. Multiple antiepileptic drug therapies harbour the risk of serious side effects as demonstrated in our patient. Valproate-induced encephalopathy is a rare but serious complication especially in older people. An increased risk in the

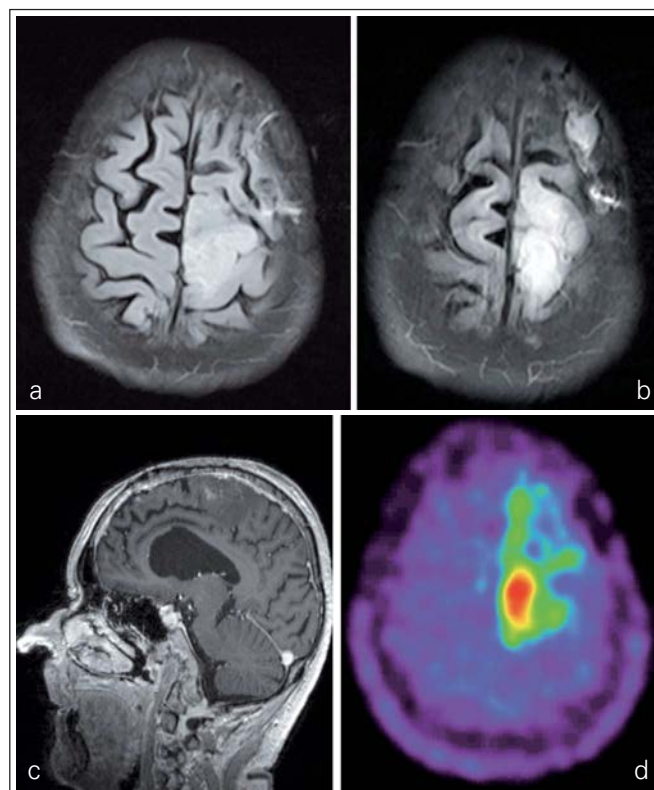


Figure 1: (a, b) MRI: FLAIR; (c) T1 with contrast media showing hyperintense cortical and subcortical signals with contrast enhancement at the left central region. (d) FET-PET increased FET metabolism in the left central region.

presence of topiramate is reported and may be a causative factor in this case [2].

Chemotherapy can positively affect seizure control in low-grade gliomas with or even without radiological signs of tumour response [1, 3, 4]. This treatment option can be taken into account especially in patients with uncontrolled seizures.

Some remarks on this case are necessary. Nowadays, early radiotherapy of low-grade glioma is not the standard of care. Moreover, today 50 Gy are recommended in low-grade glioma in order to reduce late toxicity as occurred in our patient with a high dose of 60 Gy (radionecrosis and white matter changes after 21 years). Surveillance at a centre with both epilepsy and neuro-oncology expertise is crucial in such patients.

During treatment with temozolomide, cognition as well as gait improved and the patient has been on therapy for 2 months with a KPS of 70.

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Primary CNS Lymphoma: An Unusual Case of Prolonged Response to Steroids and Extended Survival (21 Years)

Chiara Bosa, Luca Bertero, Elisa Trevisan, Roberta Rudà

From the Department of Neuro-Oncology, University and Città della Salute e della Scienza, Turin, Italy

■ Case Report

In 1991, a 27-year-old man presented at the emergency department of a country hospital with diplopia, tickling paraesthesia, and a right-sided hemiparesis. He underwent contrast-enhanced brain MRI which documented a lesion with inhomogeneous enhancement in the right paramedian pontine region. Other examinations (CSF analysis with isoelectric focussing, EMG, SSEP) were negative and steroids (dexamethasone 8 mg/d) were then administered with clinical improvement.

The MRI examinations at 1 and 6 months after steroid therapy were stable and the patient remained asymptomatic.

In 2007, 16 years after the first episode, the man was admitted to our hospital with dizziness and diplopia. Contrast-enhanced MRI showed multiple enhancing areas in the right cerebellar hemisphere, the floor of the fourth ventricle, and the mesencephalic-diencephalic region. The original pontine lesion on brain MRI was unchanged and spine MRI was normal (Figures 1A, 1B). The patient was extensively investigated (systemic work-up and CSF analysis), and the spectrum of steroid-responsive non-neoplastic lesions in the CNS (multiple sclerosis, neurosarcoidosis, Behçet disease, and atypical tuberculosis) was ruled out. Primary central nervous system lymphoma (PCNSL) was then suspected. An HIV serum test was negative. The patient refused a biopsy, then was treated

Figure 1: T1-weighted MR images with gadolinium at first relapse in 2007.

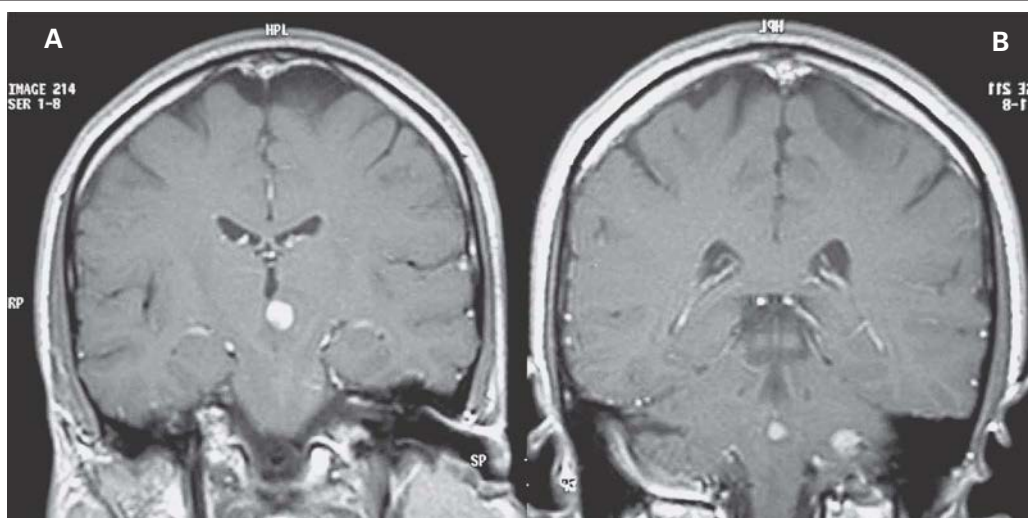
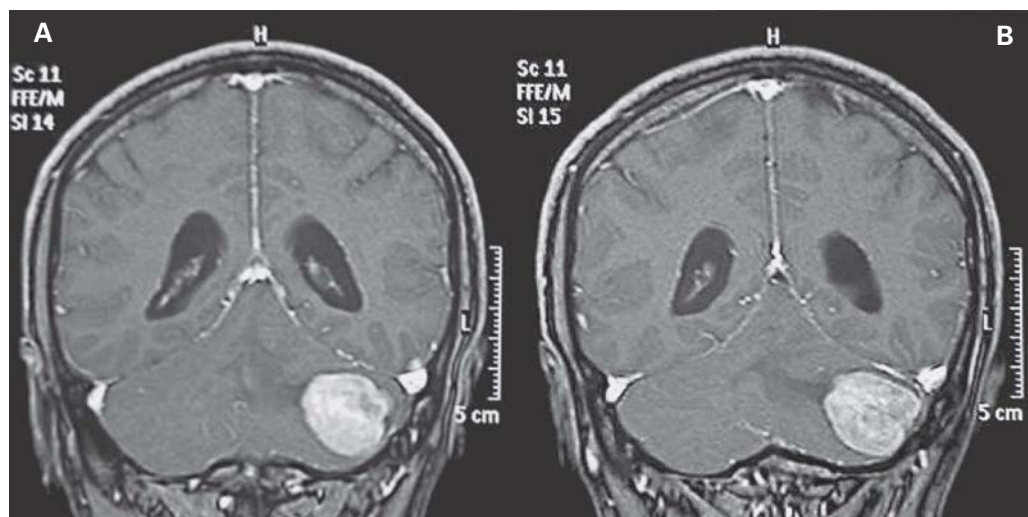


Figure 2: T1-weighted MR images with gadolinium at second relapse in 2009.



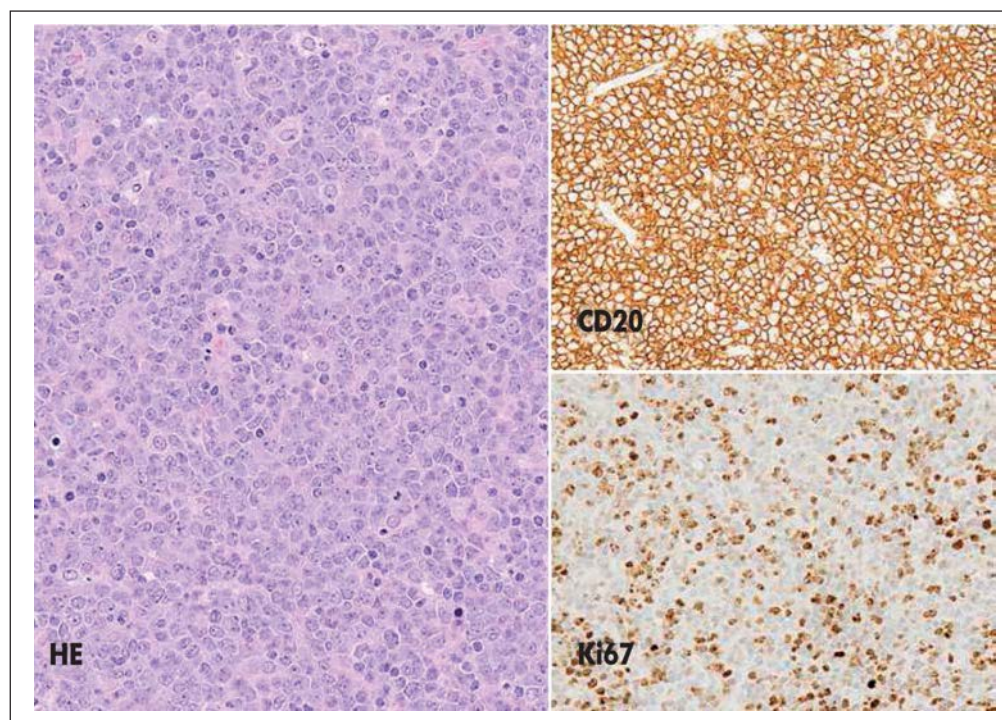


Figure 3. Hematoxylin and eosin staining, CD20 staining, and Ki67 staining.

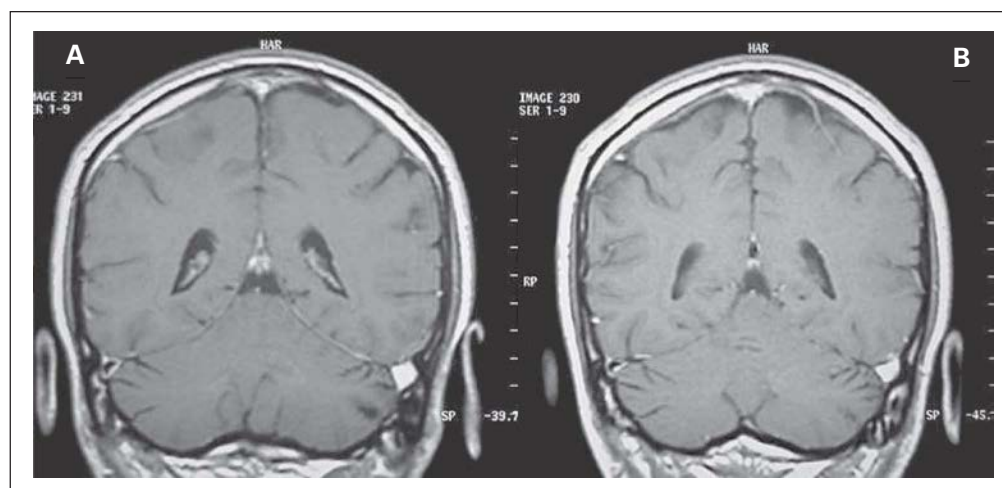


Figure 4: T1-weighted MR images with gadolinium after treatment with high-dose methotrexate and whole-brain radiotherapy.

with steroids and complete clinical and radiological remission was achieved.

In April 2009, at the age of 45, the patient presented again at the emergency department with headache, vomiting, and dizziness. We performed contrast-enhanced brain MRI which showed a new, large enhancing lesion in the left cerebellum with distortion of the fourth ventricle but no evidence of hydrocephalus (Figures 2A, 2B).

The lesion was surgically partially resected and the histological diagnosis was that of diffuse large B-cell lymphoma (Figure 3). The examinations performed for the staging of lymphoma (contrast-enhanced spine MRI, CSF analysis, chest-abdomen CT scan, whole-body PET scan, testicular ultrasound, and bone marrow biopsy) ruled out systemic involvement.

The patient started chemotherapy with high-dose methotrexate (3.5 gr/m² body surface every 2 weeks). He com-

pleted 6 cycles with good tolerance and nCR (near complete response) on MRI. Whole-brain radiotherapy (WBRT; 36 Gy + boost of 9 Gy) was then performed. At the first brain MRI performed after the end of treatment (December 2009) complete response was observed (Figures 4A, 4B) and subsequent serial MRI examinations showed no recurrence (last MRI performed in January 2012). The patient is now neurologically normal without cognitive deficits and is continuing follow-up with MRI every 6 months.

Comment

Primary CNS lymphoma, when affecting young and immunocompetent subjects and being located in critical areas for biopsy, can present diagnostic problems at onset. Treatment with steroids can lead to a regression of lesions in up to 40 % of patients, thus deferring the definite histological diagnosis.

Our case shows some peculiar features: a long disease history (overall, 21 years) with multiple recurrences involving exclusively the brain stem, cerebellum, and thalamus; an unusual and protracted response to steroids

alone and complete response to standard chemo- and radiotherapies even if performed very late (18 years after the onset of symptoms).

Further Reading:

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Psychosocial Care for Neuro-Oncology Patients, Results of a Survey on Behalf of EANO

Hanneke Zwinkels

■ Introduction

Patients with malignant brain tumours are confronted with a disease with a poor perspective and hardly any chance for cure. With poor prognosis and possible cognitive and physical decline brain tumours affect quality of life and this reflects a need for psychosocial and supportive care. Clinicians responsible for treatment within a multidisciplinary team are able to refer patients and their partners for psychosocial care to oncology nurses, social workers, (neuro-) psychologists, physiotherapists, and speech therapists. These health care professionals can play a key role by guiding patients and their family carers from diagnosis until death, paying attention to the side effects of treatment and its influence on quality of life. Although this supportive care is still limited to certain medical centres, there is increasing interest in neuro-oncology as a sub-specialty for other health care professionals. EANO would like to encourage collaborations between different specialties and the focus on the availability of supportive care.

■ Background

A lot of – mostly observational – studies reflect the increasing attention for supportive care needs in patients with brain tumours. Recently, 2 reviews were published describing the knowledge on patients' psychosocial needs and the type of care that has been found to be beneficial. Looking at the patient's and caregiver's perspective, Sterckx et al [1] state that both patients and caregivers report many emotional, instrumental, and informational needs, but that they are dissatisfied with the received support or because of lack of adequate support. From a clinical perspective, Ford et al [2] conclude that there is a need to refine understanding of patients' and caregivers' experiences and needs, and to better tune care to their needs.

But do we know which care is available and where? From a UK study in which clinicians from multidisciplinary neuro-oncology teams were approached to get insight into available care, it became clear that more than 80 % of the respondents (n = 86) reported having referral access to neurologists, physiotherapy, speech therapy, and clinical trials. Fewer clinicians (60–70 %) were able to refer to an epilepsy nurse, a social worker, counsellor, neuropsychologist or support group, or for rehabilitation, occupational therapy, or complementary therapies. The least accessible service was clinical psychology (50 %) [3].

■ Methods

On behalf of EANO, e-mails were sent out to its members with the aim to evaluate which health care professionals provide this supportive care in an attached survey. In this way,

clarity on the available supportive care throughout Europe could be established. Analysis of the received surveys was performed with SPSS 17.0.

■ Results

Approximately 350 e-mails were sent, which resulted in received surveys on delivered psychosocial care from 60 health care professionals (HCP); 20 % were clinicians, 42 % nurses, 10 % social workers, 18 % psychologists, 6 % neuropsychologists, 2 % speech therapists, and 2 % physiotherapists. The number of respondents per country: the Netherlands 24 (13 nurses), United Kingdom 8 (7 nurses), France 7 (2 nurses), Italy 6 (1 nurse), Belgium 4, Germany 3 (1 nurse), Spain 3, Sweden 2, Denmark 2 (1 nurse), and, finally, Austria 1. The mean age of clinicians (n = 12) was higher than that of nurses, the mean age of nurses (n = 25) was higher than the mean age of paramedical HCPs (n = 23).

Most HCPs provide care for patients with primary as well as secondary brain tumours (78 %), whereas 3 % only provide care for secondary brain tumours. 40 % of the HCPs provide care for patients with spinal cord tumours while 33.3 % do so occasionally. 25 % of the total respondents provide care for children.

Psychosocial and supportive care most importantly consist of support and information on symptoms and conditions, social aspects and coping; to a certain extent, other aspects such as medication, anti-epileptic drugs, anxiety and depression, end-of-life phase situations and existential problems were mentioned (Table 1), depending on the profession of the HCP. In all surveys received from nurses, psychosocial and supportive care was offered for both patients and their partners, other HCPs such as physiotherapists and psychologists mainly support patients.

Both nurses and paramedical HCPs provide psychosocial support for end-of-life and existential issues, 84 % of nurses (n = 25)

Table 1. Various provider groups and their spectra of support and information.

	Information of patient on disease		Patient care during end of life		Supportive care on existential problems	
	No	Yes	No	Yes	No	Yes
Nurse/nurse practitioner	1	24	4	21	3	22
Health care provider	13	10	10	13	3	20
Clinician	0	12	5	7	6	6
Total	14	46	19	41	12	48

compared to 56 % of paramedical HCPs (n = 23) provide care during the end-of-life phase. Two nurses practice in a home care setting, all other HCPs work at an academic or non-academic hospital.

■ Conclusion

The results of the received surveys show that in Western Europe there are multidisciplinary teams providing psychosocial care, in the Netherlands and the UK there are more nurses than other health care professionals available for this type of care. However, the e-mails sent out were sometimes undeliverable (approximately 60 of 350), and EANO has less members in Eastern Europe. The results described do not give enough insight into available psychosocial care in Europe, however, for Western European countries it seems that there are more HCPs available.

■ Recommendations

Psychosocial oncology focuses on a whole-person approach to cancer care, addressing the social, psychological, emotional, spiritual, and functional aspects of the patient journey through a multidisciplinary team and service providers from various care settings. The disciplines include oncology, nursing, social work, nutrition, psychology, palliative care, psychiatry, rehabilitation, volunteer services, and spiritual care. Psychosocial oncology is an essential service to improve the quality of life for people affected by cancer. The availability of health care professionals working in multidisciplinary neuro-oncology teams could be increased to improve psychosocial neuro-oncology.

Neuro-oncology specialist nurses play a key role by acting as a point of contact for patients, their caregivers, and all other healthcare professionals involved in the clinical management of brain tumour patients. Oncology nurses are the professionals most often available for patients and families as they experience cancer across all settings of care. Oncology nurses play a fundamental role in cancer care, with the potential to influence and improve the quality of care. The position of the neuro-oncology nurses in the multidisciplinary setting is not clearly defined, although their role is recognized as being valuable and expanding. To improve care and care management of neuro-oncology patients development of expertise and education of neuro-oncology nurses is essential [4].

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The Role and Support of Caregivers: We Also Ride the Brain Tumour Roller Coaster

Kathy Oliver

"It's like standing on the shore watching him out at sea. Sometimes the waves bring him back closer to me and sometimes the tide takes him away again."

These words, written by a caregiver, hauntingly capture the emotional ups and downs of looking after a person with a malignant brain tumour. Brimming with pathos, tinged with strain, and symbolic of a journey that is unique in the atlas of diseases, these 2 simple sentences highlight the fact that caregivers also ride the brain tumour roller coaster.

One of the most striking things about brain tumours is that, unlike other cancers, they intersect 3 major disease areas: cancer, neurological disease, and rare disease. This triumvirate presents a huge challenge to both the patient and the caregiver.

■ Understanding the Caregiver's Perspective

The stresses resulting from a brain tumour diagnosis are significant and fairly well-documented for patients. But the effects of this devastating diagnosis on the caregiver were historically not so widely understood or recognised.

In recent years, however, there have been a number of studies focussing on the brain tumour caregiver's role, especially with regard to high-grade glioma.

A team from the Department of Oncology at the University Hospital in Leuven, Belgium, led by Wendy Sterckx, carried out a systematic review from the patient's and caregiver's perspectives on the impact of a high-grade glioma on everyday life. The results were published in the *European Journal of Oncology* in 2012 [1]. The review states:

"Caregivers associate the diagnosis [of a brain tumour] with a loss of safety in daily life. Suffering and powerlessness loom large ... Feelings of being overwhelmed, denial, anger and isolation are described. In an attempt to cope with the diagnosis, caregivers take every day as it comes and do not want to plan ahead. They try to prepare themselves for the worst and want to be ready for when the patient deteriorates."

This same Leuven review mentions that the patient's cognitive and neuropsychiatric symptoms are the greatest challenges for caregivers.

Furthermore, the paper quotes other studies – notably Fox and Lantz, Sherwood et al, Janda et al, and Schubart et al – when it reports:

"[A brain tumour] is a family disease. Caregivers' distress is reflected in burden and depressive symptoms, both related to the reduced independence and neuro-psychiatric symptoms of the patient. Compared with caregivers of other brain tumour patients, caregivers of patients with a glioblastoma have a worse quality of life and may have more psychosocial needs because the disease process is faster and they have less time to adapt."

A 2010 Australian study of high-grade glioma brain tumour caregivers from a team in Perth pointed out that:

"... Caregivers in this study reported experiences similar to those described by caregivers of people with other cancers. What differed for this group [of brain tumour caregivers] was the rapidity of change and the need for immediate information and support to assist with caring for a person with high grade glioma" [2].

■ Living the New Normal

After diagnosis, brain tumour patients and their caregivers must try to rebuild their lives and learn to live the "new normal".

For the caregiver this may include a major readjustment in family dynamics and roles. Caregivers may have to learn how to move and handle a patient, organise equipment, monitor and administer medications, become the family's main transport person, oversee the patient's personal care, and help the patient cope with treatment side effects.

Caregiving can be incredibly intense and extremely isolating. On the other hand, many caregivers have also said that the inspiration and courage shown by the brain tumour patient may bring them to a new level of deep love, admiration, and closeness with the patient. Time together is cherished in a way that it has never been before.

■ Caregivers and the IBTA Survey

The International Brain Tumour Alliance (IBTA) carried out a patient and caregiver satisfaction survey in 2010 which asked: "Was information about your diagnosis and prognosis provided to you in a considerate and sensitive manner and in a suitable physical environment?" [3].

Although 59 % of those surveyed responded "yes", a number highlighted less than satisfactory situations. They included a lack of compassion shown by medical staff, bad news being broken in inappropriate surroundings, and a nihilistic attitude on the part of doctors.

One respondent wrote:

"We did not understand the terminal prognosis, it was not properly explained ... [This was] harmful to the surviving partner as expectations were not properly set. The surviving partner is a 'patient' in this sense also, but is not treated as such. I think there is a need for counselling being given to the partner-carer in parallel with the treatment for the patient."

■ Helping Caregivers Cope

So what can caregivers do to help themselves cope on this journey?

Information, befriending, and support for caregivers is available from brain tumour charities. However, not every country is fortunate enough to have these organisations. A directory of brain tumour charities known to the IBTA is available at

www.theibta.org/websitelinks.html

A 2012 article in *Brain Tumour* magazine by Dr Martin Klein of the VU University Medical Center in Amsterdam says:

"Research to date indicates that, while continuing to face significant caregiving stress, caregivers can benefit greatly from structured psychosocial interventions, leading to clinically significant improvements in the caregiver's quality of life."

We at the IBTA have seen that it may be useful for families, if they wish, to be paired in a buddy system with other families on the same journey so there is peer-to-peer support. This is something that brain tumour patient support groups often facilitate. But unfortunately, not all families are put in touch with these groups by clinicians at the time of diagnosis.

Some neuro-oncology departments run their own support group meetings which facilitate such introductions. In many cases, it is the specialist neuro-oncology nurses who run these groups.

Klein also mentions the use of

"... E-Communities by which caregivers are connected to their peers ... over the Internet."

There are, in fact, a number of highly regarded, reliable web resources for brain tumour caregivers.

Used by patients and caregivers worldwide, the US-based Musella Foundation's website – www.virtualtrials.com – houses a section on survivors' stories which can help give people hope. The website also hosts a number of excellent

online discussion groups where patients and caregivers can find information, support, friendship, and understanding.

The Cancer Institute New South Wales (Australia) website features an excellent set of 16 brain tumour fact sheets and 11 resource sheets. These cover topics such as anger management, stress, concentration, communication, and fatigue, and are not just aimed at the brain tumour patient but at the caregiver as well.

■ Lessons Learned

There is no exact science to caregiving. It seems to hover somewhere between treading on eggshells, juggling dozens of balls at once, and having unlimited reservoirs of physical and mental strength.

As one of the caregivers to our son Colin for over 7 years, until he died in August 2011 from his brain tumour, I learned many lessons.

I learned that caregiving must be a partnership so that the patient can make his or her own decisions and choices as much as possible in order to feel that they are still in control.

I learned that it is also vital not to forget the needs of other people in the family; to accept help from relatives, friends, and neighbours when they offer it; to maintain continuity and as much of a sense of normality as possible.

Finally, I learned that the hope and encouragement you give as a caregiver to the patient can go a long way in helping alleviate some of the nightmarish aspects of the brain tumour journey. As Dr Jerome Groopman, a leading cancer researcher, said:

"Hope acknowledges the significant obstacles and deep pitfalls along that path. True hope has no room for delusion. ... Hope gives us the courage to confront our circumstances and the capacity to surmount them" [4].

Notes:

1. Sterckx W, Coolbrandt A, Dierckx de Casterlé B, et al. The impact of a high-grade glioma on everyday life: a systematic review from the patient and caregiver perspective. *Eur J Oncol Nurs* 2013; 17: 107–17.
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Calendar of Events

2013

February 24–27	Intraoperative Imaging Society (IOIS) 4th Annual Meeting	St Louis, MO, USA	http://www.soc-neuro-onc.org/en/cev/90
March 4–8	Neurosurgery Week	London, UK	http://www.rcseng.ac.uk/courses/course-search/neurosurgery-week
March 21–23	19th Annual Blood-Brain Barrier Consortium Meeting	Stevenson, WA, USA	http://www.ohsu.edu/xd/research/centers-institutes/neurology/blood-brain-barrier/news-and-events/meeting2013.cfm
March 21–24	10th Meeting of Asian Society for Neuro-Oncology jointly with the 5th Annual Meeting of Indian Society of NeuroOncology	Mumbai, India	http://www.asno2013.org/?utm_source=MailingList&utm_medium=email&utm_campaign=ENewsDec2012
March 22–23	EORTC EANO ESMO 2013: Trends in Central Nervous System Malignancies	Prague, Czech Republic	http://www.ecco-org.eu/Conferences/Conferences/EORTC_EANO_ESMO.aspx
April 4–6	XXIV Congreso Sociedad Latino-americana Oncología Pediátrica	Bogota, Colombia	http://www.theibta.org/LatinAmerican2013.pdf?utm_source=MailingList&utm_medium=email&utm_campaign=ENewsDec2012
April 6–10	American Association for Cancer Research Annual Meeting	Washington, DC, USA	http://www.aacr.org/
April 10–11	AHNS 2013 Annual Meeting during the Combined Otolaryngology Society Meetings	Orlando, USA	http://www.ahns.info/meetings/index.php
April 12–13	3. ASORS-Jahreskongress Supportive Therapie und Rehabilitation bei Krebs	Berlin, Germany	http://www.kongresseonline.de/ASORS_2013/html/impressum.html
April 17–20	3rd International CNS Germ Cell Tumour Symposium	Cambridge, UK	http://www.cclg.org.uk/events/3rd-international-cns-germ-cell-tumour-symposium-2
May 9–12	19. Jahreskongress der Deutschen Gesellschaft für Radioonkologie	Berlin, Germany	http://www.degro.org/degro2013/
May 16–17	2013 Pediatric Neuro-Oncology Basic and Translational Research Conference	Ft Lauderdale, FL, USA	http://www.soc-neuro-onc.org/en/cev/88
May 27–30	16th Quadrennial Meeting of the World Society for Stereotactic & Functional Neurosurgery	Tokyo, Japan	http://www.soc-neuro-onc.org/en/cev/89
May 29–June 1	Interventional Oncology Sans Frontières (IOSFC): Creativity, Novelty, and Clinical Excellence	Cernobbio, Italy	http://www.ecco-org.eu/Global/Events/Other-Events/IOSFC2013.aspx
May 30–June 2	13th World Congress of the European Association for Palliative Care	Prague, Czech Republic	http://www.eapc-2013.org/
May 31–June 4	2013 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
June 7	The Brain Tumor Biotech Summit	New York, NY, USA	http://www.braintumorbiotechsummit.org/
June 8–14	North American Association of Central Cancer Registries (NAACCR) 2013 Annual Conference	Austin, TX, USA	
June 22–28	Methods in Clinical Cancer Research	Flims, Switzerland	http://www.ecco-org.eu/Education/Clinical-trials-workshop/Flims-workshops/FLIMS-15.aspx
June 24–25	Cancer and Metabolism 2013	Amsterdam, The Netherlands	http://www.ecco-org.eu/Global/Events/Other-Events/Cancer-and-Metabolism-2013.aspx
September 4–7	XXIV Brazilian Congress of Neuro-physiology	Rio de Janeiro, Brazil	http://www.kenes-group.com/Events/xxiv-brazilian-congress-of-neurophysiology/
September 8–13	XV WFNS World Congress of Neuro-surgery	Seoul, South Korea	http://www.wfns2013.org/
September 21–26	XXI World Congress of Neurology	Vienna, Austria	http://www.wcn-neurology.com
September 27–29	Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology 2013 International Cancer Care Symposium	Berlin, Germany	http://www2.kenes.com/mascc2013/Pages/Home.aspx

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IMPORTANT DATES

Deadline Abstract submission: 11 February 2013

For further information and to view the Scientific Programme:
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Interview with Dr Florence Laigle-Donadey about the “Surgery versus Biopsy for Potentially Operable GBM in the Elderly” trial

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dear Dr Laigle-Donadey, can you tell us about the ongoing “Surgery versus Biopsy for potentially operable GBM in the elderly” trial? I guess this is one of the first randomised trials to assess the role of resection in a specific GBM population. What is the rationale and background for this trial?

A: The incidence of gliomas is increasing in the elderly population. The lack of robust guidelines issued from clinical trials in this population may lead to an inappropriate pattern of care, left to the discretion of the responsible physician. This is particularly true for surgical decisions in this age group, as we know there is a very heterogeneous pattern of neurosurgical care for these patients in France and other countries.

Indeed, it is often believed that elderly patients recover more slowly from surgery and are at a higher risk for post-operative neurologic deterioration. Nevertheless, retrospective studies have found that resection of primary brain tumours could be performed safely in older patients with a positive impact on survival, especially after complete resection.

To date, the value of debulking surgery for GBM in the elderly has been shown in a small Finnish randomised clinical trial reported by Vuorinen et al, in which 23 patients aged > 65 years with malignant glioma (83 % with GBM) were randomly assigned to biopsy only or to surgical resection, followed by radiotherapy. Median survival time was significantly longer with resection (5.6 months) compared to 2.8 months with biopsy. When compared to biopsy, resection was also associated with improved quality of life. These data are encouraging, but they are preliminary because of the very small number of evaluated patients.

A large prospective randomised study evaluating the impact of surgery of malignant gliomas on survival and quality of life in elderly patients is strongly needed and we decided to conduct it.

Q: How is the study designed and what are the inclusion criteria?

A: Inclusion criteria are patient age ≥ 70 , a radiological pattern of probably high-grade glioma and candidacy for surgical treatment with a preoperative KPS > 50.

Q: What is your definition of the elderly? Why did you choose the age of 70 as a cut-off?

A: We chose 70 years as cut-off for homogeneous purposes because this age is conventionally chosen by French teams regarding elderly patients suffering from malignant gliomas

(confer previously published studies such as RSP [Keime-Guibert F, et al] and TAG [Gállego Pérez-Larraya J, et al]).

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

A: This is a national French trial supported by the Association des Neuro-Oncologues d’Expression Française (ANOCEF) and by Assistance Publique Hôpitaux de Paris (AP-HP). Overall, there are 12 participating institutions in France.

Q: Recent studies focusing on the treatment of GBM in the elderly population have revealed important results and your study will give more information about this disease. Can you critique the rationale of your study, taking into account the results of these studies?

A: Obviously, there is a great dynamism of clinical research in the elderly population, and a lot of emerging publications; I will not comment on recent works in radiotherapy and chemotherapy in this population but I just will focus on surgical studies: Ewert et al recently showed that the extent of microsurgical resection for patients treated with adjuvant radiotherapy and chemotherapy seems to be predictive of a better outcome. This month, Grossmann et al showed that awake-craniotomy is a well-tolerated and safe procedure even in elderly patients and that gross total resection in elderly patients with high-grade gliomas was associated with prolonged survival. However, all these data were based on retrospective analyses and it is crucial to confirm prospectively the role of surgery by means of a study such as ours.

Q: Is there any translational or biological component to this trial?

A: Yes, there is an accompanying translational research package to this trial. We are searching for the usual diagnostic, prognostic, and predictive biomarkers.

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

A: It is a very difficult study to conduct, because it is a huge challenge for patients and their families to participate in a randomised trial with 2 very different procedures (on the one hand a “simple” biopsy and on the other hand debulking surgery). To date, we have accrued 66 of the 135 required patients according to the design of the study. We do not expect first preliminary results within the next 2 years.

Thank you very much!

Further Reading:

Ewelt C, Goeppert M, Rapp M, et al. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. *J Neurooncol* 2011; 103: 611–8.

Gállego Pérez-Larraya J, Ducray F, Chinot O, et al. Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. *J Clin Oncol* 2011; 29: 3050–5.

Grossman R, Nossek E, Sitt R, et al. Outcome of elderly patients undergoing awake-craniotomy for tumor resection. *Ann Surg Oncol* 2012 [Epub ahead of print].

Keime-Guibert F, Chinot O, Taillandier L, et al.; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 2007; 3: 1527–35.

Vuorinen V, Hinkka S, Färkkilä M, et al. Debulking or biopsy of malignant glioma in elderly people – a randomised study. *Acta Neurochir (Wien)* 2003; 145: 5–10.

Dr Florence Laigle-Donadey is the national referent investigator (along with Philippe Cornu, the national neurosurgeon coordinator) of the trial entitled, “Surgery versus Biopsy for Potentially Operable GBM in the Elderly”.

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Hotspots in Neuro-Oncology

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

■ Radiotherapy and Temozolomide in Anaplastic Astrocytoma: A Retrospective Multicenter Study by the Central Nervous System Study Group of AIRO (Italian Association of Radiation Oncology)

Scoccianti S, et al. Neuro Oncol 2012; 14: 798–807.

Too many neuro-oncologists change their personal standards of care over time without adequate support from clinical trials. A classical example for this observation is the increasing use of temozolomide in addition to radiotherapy in the first-line treatment of anaplastic astrocytoma. The largest recent trial in that patient population, the German NOA-04 trial, had compared radiotherapy alone with alkylating agent chemotherapy alone and found no difference between these 2 treatments for any endpoint. In the June issue of *Neuro-Oncology*, an Italian consortium reported a retrospective study of 295 patients with newly diagnosed anaplastic astrocytoma treated from 2002–2007. All patients had received radiotherapy, 67 % received postoperative temozolomide. The majority had both concomitant and adjuvant temozolomide. The increasing use of temozolomide over the time frame covered did not produce an improvement in survival. This interesting analysis emphasizes the need to base changes in standards of care on adequate randomized trials. At present, the ongoing CATNON trial is closest to answering the question of whether anaplastic astrocytoma patients should be treated with combined modality treatment upfront.

■ Clinical and Molecular Characteristics of Congenital Glioblastoma

Macy ME, et al. Neuro Oncol 2012; 14: 931–41.

In the July issue, a rare variant of glioblastoma, congenital glioblastoma, was studied and reviewed. The authors reported an analysis of 5 such patients, 1 died at surgery, the other 4 patients had adequate tumour control with a median progression-free survival of 36 months (range: 30–110 months) with chemotherapy alone. There were no characteristic patterns on molecular characterization using Affymetrix microarrays and exhibited expression profiles related both to paediatric and adult glioblastoma.

■ Incidence, Treatment and Survival of Patients with Craniopharyngioma in the Surveillance, Epidemiology and End Results Program

Zacharia BE, et al. Neuro Oncol 2012; 14: 1070–8.

Craniopharyngioma is a rare brain tumour which may occur in almost any age group and where treatment decisions are

often controversial, specifically regarding the extent of resection and the role and timing of radiotherapy. In the August issue, Zacharia et al presented an overview of 644 patients with craniopharyngioma diagnosed between 2004 and 2008 with data derived from the Surveillance, Epidemiology and End Results program (SEER) database. One- and 3-year survival rates were 92 % and 86 %. On multivariate modelling, younger age, smaller tumours, subtotal resection, and administration of radiotherapy were favourable prognostic factors, whereas black race was associated with less favourable outcome. Altogether, this publication provides a contemporary overview on the incidence, clinical presentation, and current patterns of care for this rare brain tumour which may serve well for the design and conduct of future clinical trials in this disease.

■ Phase II Trial of Lapatinib in Adult and Pediatric Patients with Neurofibromatosis Type 2 and Progressive Vestibular Schwannomas

Karajannis MA, et al. Neuro Oncol 2012; 14: 1163–70.

Medical treatment options for patients with neurofibromatosis type 2 (NF2) and schwannomas progressing after surgery and radiotherapy are scarce. In the September issue, Karajannis et al reported the results of a single-institution phase-II study to assess the response of patients affected by these tumours to lapatinib, a reversible inhibitor of epidermal growth factor receptor and ErbB2. Response was defined as a > 15-% decrease in tumour volume. This endpoint was evaluable in 17 patients. Hearing performance was available as a secondary endpoint in 13 patients. Four of 17 available patients showed an objective response with a median time to response of 4.5 months. Four of 13 patients available for hearing had a response, too. Toxicity was in general minor and no modifications of the dose of 900 mg/m² twice daily (paediatric patients), respectively 1500 mg flat daily for adult patients were made. Overall, this study demonstrates some objective activity of lapatinib in NF2 patients with progressive vestibular schwannomas. While this efficacy is limited, it adds to the current repertoire of pharmacological agents with some benefit in these patients that are notoriously difficult to treat. Combinations of lapatinib with vascular endothelial growth factor antagonists seem to be the next step.

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A Forum for Sharing the Latest Laboratory and Clinical Research: 17th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology

Nicholas Butowski

The 17th Annual Scientific Meeting of the Society for Neuro-Oncology was held November 15–18, 2012, in Washington, DC. We thank Drs E Antonio Chiocca, Balveen Kaur, Vinay Puduvalli, and Michael Glantz for composing a comprehensive programme highlighting cutting-edge laboratory and clinical research in the field of neuro-oncology. The meeting resulted in a stimulating exchange of ideas among neuro-oncologists, medical oncologists, neurosurgeons, neuropathologists, radiation oncologists, neuroradiologists, paediatricians, laboratory scientists, nurses, and other specialists involved in the research, diagnosis, care, and treatment of patients with tumours of the central nervous system. In addition to the thought-provoking Education Day and the abstract-driven scientific sessions of the main meeting, SNO offered a number of innovative features at the 2012 meeting, including a special biomarkers course, a keynote address from Dr Bert Vogelstein, a new Public Service Award, the inaugural Abhijit Guha Award and Lecture, expanded sessions for Young Investigators, and an evening satellite symposium on 1p/19q co-deleted anaplastic gliomas.

■ Education Day

The meeting began on Thursday, November 15, with an opportune and relevant programme for the Education Day consisting of concurrent morning sessions entitled “Targeted Therapies Against Primary Brain Tumours” and “Quality of Life/Symptom Management”. The afternoon session offered a novel programme titled “SNO Course on the Basics of Biomarkers 2012”.

■ SNO Annual Meeting

The formal meeting launched on Friday, November 16, with Sunrise Sessions on the following topics: (1) EANO and SNO Joint Session: From Guidelines to New Trials in Low-Grade Gliomas: The American and European Views, (2) NF2 Update: Hearing Restoration and Foundations for the Future, (3) Energetics and Metabolism, and (4) Re-engineered T Cells and Bone Marrow Cells. The first plenary session began with an official meeting welcome by Dr Chiocca followed by a Public Service Award presented to Edward Shaw and by presentation of top-Scoring Abstracts. Subsequent to these events the first Abhijit Guha Award was bestowed to James Rutka, and we heard an invigorating keynote lecture given by Bert Vogelstein.

A Young Investigators Luncheon Roundtable was held at noon on Friday at which trainees and early-phase independent investigators participated in informal discussions with senior investigators at roundtables organized into a variety of differ-

ent areas. Afternoon concurrent sessions included (1) Medical, Neuro- and Radiation Oncology and (2) Basic Sciences. The next set of concurrent sessions included (1) Symptom Management, Neuro-cognitive and Quality of Life; and (2) Molecular Epidemiology, -Omics, and Prognostic Markers. After an exciting, first of its kind, town-hall style meeting on the management of 1p/19q co-deleted anaplastic gliomas, the evening opened for poster sessions, which was an opportunity for lively discussion and debate.

Saturday, November 17, Sunrise Sessions featured the following topics: (1) Asian Society for Neuro-Oncology Session, (2) The CMV and Glioma Connection, (3) Mechanisms of Glioblastoma Immuno-evasion, and (4) Pituitary Tumours: Biology and Treatment. Next in line was the presentation of the Victor Levin Award and Lecture by Gregory Cairncross and Robert Jenkins. The first afternoon concurrent sessions were (1) Cell Biology/Signalling and Epidemiology or (2) Pathology and Radiology with subsequent afternoon concurrent sessions on (1) Angiogenesis/Invasion and (2) Surgery and Immunology. The second lively poster session took place after the oral sessions concluded for the day. That evening, the SNO Banquet beheld itself as the social highlight of the meeting.

Sunday, November 18, witnessed the first SNO highlights session – an invitation-only press programme that highlighted new advances in neuro-oncology, major trial results, and significant advances in supportive care and patient quality of life. Sunrise Sessions included (1) Oncolytic Viruses: Clinical Trials Update, (2) The Radiobiology of CNS Tumours, (3) The Biology of Brain Metastases, and (4) MicroRNA Biology in CNS Tumours. These were followed by a plenary session presenting Top Scoring Abstracts and a RANO session prior to the meeting adjournment.

We look forward to seeing members of EANO at the 4th Quadrennial Meeting of the World Federation of Neuro-Oncology in conjunction with the 18th Annual Scientific Meeting of the Society for Neuro-Oncology next November 21–24, 2013, in San Francisco, California.

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