Hotspots in Neuro-Oncology

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Management of Treatment-Associated Toxicities of Anti-Angiogenic Therapy in Patients with Brain Tumors


Antiangiogenic therapies have become the most intense area of clinical research in the treatment of malignant gliomas. Introduction of such agents has altered the risks and side effects of overall glioma treatment, and it is unclear in what way the addition of antiangiogenic compounds modifies the safety and tolerability of additional treatment such as radiation or chemotherapy. In the light of these novel developments, it is appropriate to review the management of such treatment-associated toxicities in glioma patients as done in an authoritative review by Armstrong et al, published in the October issue. Specifically, the authors address how to deal with hypotension and proteinuria, wound healing, and the presumably increased risk of thromboembolic events in patients treated with antiangiogenic compounds. The authors also provide recommendations for the diagnosis, monitoring, and management of such complications. Since antiangiogenic compounds will stay with us in neuro-oncology for some time, this review is worthwhile to read to be up to date in a field that is gaining increasing importance in clinical neuro-oncology.

Glioblastoma Resistance to Anti-VEGF Therapy Is Associated with Myeloid Cell Infiltration, Stem Cell Accumulation and a Mesenchymal Phenotype


According to a press release by Roche (Basel, Switzerland), the registration trial for bevacizumab in the treatment of newly diagnosed glioblastoma, AVAGlio, has reached the primary endpoint of improving progression-free survival whereas no mature results for the overall survival endpoint have been made available yet. These preliminary observations underscore the urgent need to understand pathways of constitutive or acquired resistance to anti-vascular endothelial growth factor (VEGF) treatments. In the November issue of Neuro-Oncology, Piao et al from the MD Anderson Cancer Center analysed the evolution of resistance to anti-VEGF therapy, using either the VEGF antibody, bevacizumab, or the tyrosine kinase inhibitor, sunitinib, in the U87MG orthotopic human glioma model. Bevacizumab doubled survival whereas sunitinib did not. Sunitinib plus bevacizumab, was superior to bevacizumab alone. Both agents reduced tumour vascularity, but bevacizumab was more effective in inhibiting vascularity in the periphery of the tumours, and revascularization occurred earlier in sunitinib-treated tumours, associated with tumour progression. Increased numbers of CD11b+/F4/80+ cells were observed earlier in control and sunitinib-treated animals than in bevacizumab-treated animals and were associated with treatment failure. Although only one cell line model was studied, the study supports the view that a better understanding of tumour/host cell interactions might help to improve on the results obtained with angiogenesis inhibition in the clinic so far.

EORTC 26083 Phase I/II Trial of Dasatinib in Combination with CCNU in Patients with Recurrent Glioblastoma


Novel approaches to the treatment of recurrent glioblastoma are urgently needed. In the December issue, the results of EORTC trial 26083 were reported. This trial examined the combination of the Src kinase inhibitor dasatinib and CCNU in 26 patients with recurrent glioblastoma as the phase-I part of a planned multicentre, randomized phase-II trial. However, the randomized part of the trial was not initiated because of the results of this trial. Five dose levels were explored. Ten patients experienced dose-limiting toxicity which was mostly myelosuppression, with rates of grade-3-of-4 neutropenia in 26.9 % and thrombocytopenia in 42.3 %. Median progression-free survival was only 1.35 months, and only 7.7 % of the patients were free from progression at 6 months. These results are inferior compared with historical controls with CCNU alone; accordingly, EORTC 26083 did not provide any rationale to move this combination forward in the treatment of recurrent glioblastoma.

Survival and Secondary Tumors in Children with Medulloblastoma Receiving Radiotherapy and Adjuvant Chemotherapy: Results of Children’s Oncology Group Trial A9961


In the January issue, Packer et al reported very interesting results from Children’s Oncology Group trial A9961 which compared radiotherapy combined with vincristine plus adjuvant chemotherapy with platinum, vincristine, and either CCNU or cyclophosphamide. Patients were enrolled between December 1996 and December 2000. 379 eligible patients were analyzed. Five- and 10-year event-free survival rates were 81 % and 76 %, corresponding results for overall survival were 87 % and 81 %. The primary site of relapse of the primary tumour was local. Importantly, 15 patients suffered secondary neoplasms in the absence of medulloblastoma relapse after a median time of 5.8 years from diagnosis. All secondary tumours occurred in body regions exposed to radia-
tion. The high risk of secondary tumours, many of which are malignant gliomas, is of concern especially with the recent great advances in the molecular subclassification and more targeted therapy options for patients with these tumours. It is of utmost importance to revisit the current standards of care once novel, more effective agents to treat medulloblastoma, which impact survival, are introduced into clinical practice.

**Survival Meta-Analyses for >1800 Malignant Peripheral Nerve Sheath Tumor Patients with and without Neurofibromatosis Type 1**


Malignant peripheral nerve sheath tumours (MPNST) are malignant tumours derived from the peripheral nervous system that are notoriously difficult to treat. Surgery and radiotherapy remain the mainstay of therapy whereas chemotherapy is often ineffective. These tumours are strongly associated with neurofibromatosis type 1 (NF1). In the February issue, Kolberg et al performed a metaanalysis of > 1800 patients with MPNST and reviewed characteristics of 179 patients from 3 European sarcoma centres in Norway, Sweden, and Italy. Over time, they found that the traditionally assumed poorer outcome for MPNST in association with NF1 was not observed anymore in the last 2 decades possibly because of more aggressive treatment approaches to MPNST in NF1. Altogether these observations suggest that MPNST with or without NF1 may not be intrinsically different tumours and should be diagnosed, managed, and monitored accordingly. Of note, the similar outcome with or without NF1 was calculated for disease-specific survival whereas, overall, there may still be increased mortality for NF1 patients from other NF1-associated conditions. This data compilation provides a valuable basis for the planning and design of future interventional studies in NF1 and MPNST.

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