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EDITORIAL

Editorial: on the road to multi-modal and pluri-disciplinary treatment of glioblastomas

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Abstract Despite major advances in the management of malignant gliomas of which glioblastomas represent the ultimate grade of malignancy, they remain incurable. Indeed, glioblastoma patients have a median survival expectancy of only 14 months on the current standard treatment of surgical resection to the extent which is feasible, followed by adjuvant radiotherapy plus temozolomide given concomitantly with and after radiotherapy (Lefranc et al., J Clin Oncol 23:2411–2422, 2005; Expert Rev Anticancer Ther 6:719–732, 2006; Stummer et al., Neurosurgery 62:564–576, 2008). Accordingly, the present editorial discusses (1) the high cell motility and resistance to apoptosis which characterise glioblastoma growth and malignancy with respect to the failure of conventional therapy, (2) ways to overcome apoptosis resistance and the real hope offered by temozolomide, (3) targeted chemotherapeutic approaches and the disappointing results obtained in monotherapy but their potential in combination therapy, (4) anti-migratory strategies that could supplement conventional therapy notably by inhibiting a new target; the $\alpha 1$ subunit of the sodium pump, (5) dendritic cell therapy, (6) cancer stem cell targeting and finally (7) topical therapies and new surgical approaches for more radical resection which could be used to complement multi-modal treatments within a multi-disciplinary approach.

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Malignant gliomas are associated with a dismal prognosis because glioma cells can actively migrate through the narrow extra-cellular spaces in the brain, often travelling relatively long distances, making them elusive targets for effective surgical management [13, 18]. There is therefore a need for more definitive non-invasive tumour visualisation and intra-operative monitoring to permit more radical resection. Clinical and experimental data have also demonstrated that invasive malignant glioma cells show decreased proliferation rates and a relative resistance to apoptosis (type I programmed cell death) compared to the highly cellular centre of the tumour, and this may contribute to their resistance to conventional pro-apoptotic chemotherapy and radiotherapy [13]. However, as recently indicated by both Okada and Mak [24] and ourselves [13, 16], despite resistance to apoptosis being closely linked to tumourigenesis, tumour cells can still be induced to die by non-apoptotic mechanisms such as necrosis, senescence, autophagy (type II programmed cell death) and mitotic catastrophe. Provoking autophagic cell death may therefore be used to overcome apoptosis resistance. Indeed part of temozolomide's cytotoxic activity is exerted through pro-autophagic processes, at least in glioblastoma cells, via the formation of O^6-methylguanine in DNA, which mispairs with thymine during subsequent cycles of DNA replication [10, 16]. Glioma cells thus respond to temozolomide by undergoing G2/M arrest but will ultimately die from autophagy [10, 16]. Temozolomide's cytotoxic activity is also in part due to the induction of late apoptosis [28]. These actions of the compound are not contradictory because at a molecular level, apoptotic and autophagic response machineries share common pathways that either link or polarise cellular responses [14].

Hegi et al. [8] and Chinot et al. [2] have shown that patients who have glioblastomas containing a methylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter benefit from temozolomide, while those who do not are less responsive.

A prognostic factor analysis of a European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada trial [6] revealed that in patients who had tumours resected, were assigned temozolomide and radiotherapy, had had MGMT promoter status defined indicating methylated MGMT and who had a better performance status and a mini-mental state examination score of 27 or higher, were associated with improved survival [6]. Therefore, stratifying by MGMT promoter methylation status should be mandatory in all glioblastoma trials that use alkylating chemotherapy [6].

Resistance to apoptosis results from changes at the genomic, transcriptional and post-transcriptional level of proteins, protein kinases and their transcriptional factor effectors. The PTEN/ PI3-K/Akt /mTOR/NF-κB and the Ras/Raf/MEK/ERK signalling cascades play critical roles in the regulation of gene expression and prevention of apoptosis [13, 14, 16]. Components of these pathways are mutated or aberrantly expressed in human cancer, notably glioblastomas. Monoclonal antibodies and low molecular weight kinase inhibitors of these pathways are the most common classes of agents in targeted cancer treatment. Most clinical trials of these agents as monotherapies have failed to demonstrate survival benefit [32] and responses seem to be related to co-expression of epidermal growth factor receptor (EGFR) deletion mutant variant III and tumour-suppressor protein PTEN; markers that could potentially be used as predictive factors for such therapies [22]. To date, the most positive results with targeted therapy remain the high response rates with bevacizumab and irinotecan in a phase II trial for recurrent malignant gliomas [25]. The monoclonal antibody bevacizumab targets vascular endothelial growth factor (VEGF), the paracrine stimulator of angiogenesis [11, 25]. An update on survival from this trial in recurrent malignant gliomas was presented at the ASCO annual meeting in May 2008 [37]. The overall response rate for both grade III and IV was 59% (grade III, 61% and grade IV, 57%). The 6 months period free survival and overall survival for grade III were 59% and 79% and for grade IV 43% and 74%, respectively. For grade III and IV patients, the 2 year overall survival rates were 33% and 15%, respectively [37]. Therefore, the combination of bevacizumab and irinotecan provides a clinically meaningful treatment option for patients with recurrent malignant gliomas. However, combination of anti-angiogenic drugs with more potent cytotoxics will probably be necessary. Additionally, it is imperative that clinical trials which hitherto have focused largely on the intrinsic response of glioma cells to new targeted therapies, move to novel designs which are biomarker-guided to ensure better efficacy.

Another way to potentially overcome apoptosis resistance is to decrease the migration of malignant glioma cells in the brain, which should then restore a certain level of sensitivity to pro-apoptotic drugs. We have recently verified this concept in vivo on combining temozolomide with two distinct anti-migratory strategies for the treatment of athymic mice bearing a human model of glioblastoma in their brains [15, 20]. Drivers of glioma invasion include autocrine/paracrine signals. Malignant gliomas have been shown to release glutamate, which kills surrounding brain cells, creating room for tumour expansion [21]. Moreover, glioma cells are "self-propelled" and are able to adjust their shape and volume rapidly as they invade the brain parenchyma. Essential to this process is the activity of chloride channels, anion transport mechanisms [27] and aquaporins [7]. The sodium pump is another ion transporter which in addition to exchanging cations is also directly involved in the migration of cancer cells in general and of glioma cells in particular [17, 23, 33]. Accordingly, we have been the first to propose the sodium pump and more specifically its α1 subunit, which is highly expressed in glioma cells compared to normal brain tissues, as a new target in the context of malignant glioma treatment. By inhibiting sodium pump activity, it has been possible to markedly impair both glioblastoma cell proliferation and migration (through a disorganisation of the actin cytoskeleton), with marked features of autophagy as the terminal outcome [17]. A new compound targeting the α1 subunit of the sodium pump will enter Phase I clinical trials in the summer of 2008 [17].

The discovery of dendritic cells, the most potent antigen presenting cells to initiate specific immune responses and the possibility of producing them ex vivo have given rise to new protocols of active immunotherapy against gliomas [9]. Phase I clinical trials [3] have shown that vaccination using patients' peripheral dendritic cells pulsed with tumour lysates, cell fusions, RNA and/or peptides can elicit anti-tumour immune responses against central nervous system neoplasms. Although the currently available clinical data are too limited to arrive at any firm conclusions concerning its effectiveness, the advantages of dendritic cell-based immunotherapy and its documented safety and feasibility are stimulating further development and testing.

Cancer stem cells are thought to be crucial for tumourigenesis [31]. Gilbertson and Rich [5] recently reviewed data showing that the stem cells of glioblastomas are found in intimate contact with aberrant tumour vasculature. These cancer stem cells can secrete diffusible factors such as VEGF, which recruit aberrant tumour vasculature to the niche. In turn, tumour vasculature and other glioma cells

secrete factors that maintain aberrant cancer stem cell self-renewal. The targeting of such stem cells could thus present another therapeutic option.

Control of glioblastomas by topical therapy applied to the resection cavity during surgery may reduce the rate of local failure and increase the time required for localised tumour progression. These agents function inside tumour cells with microscopic and sub-microscopic precision. The only FDA-approved drug delivery system consists of carmustine (BCNU)-impregnated polymers in the form of wafers (Gliadel^{R}) [38]. These wafers are implanted into the tumour cavity during surgery and slowly release the active drug. In a Phase III trial, median survival in a BCNU wafer-treated glioblastoma group was longer (13.5 months) than in a placebo wafer-treated glioblastoma group (11.4 months). However, the comparison of the survival curves by the Kaplan–Meier method showed that the difference was not statistically significant (stratified log-rank statistics). The significance of the treatment was observed only after additional analysis [38]. Furthermore, this result was similar to the benefit derived from systemic adjuvant nitrosoureas [34]. However, to date no studies have directly compared the efficacy of systemic versus topical chemotherapy in glioblastoma. One promising surgical technique for the delivery of drugs directly into the brain parenchyma involves a convection-enhanced delivery system (CED) [30]. CED uses positive pressure infusion to generate a pressure gradient that optimises the distribution of macromolecules within the tumour and the surrounding tissue. Target tissue anatomy and catheter position are critical parameters in optimising drug delivery [30]. Using this surgical technique, a recombinant toxin (TP-38) targeting EGFR was administered to 20 patients with recurrent malignant brain tumours [29]. CED delivered intra-cerebral TP-38 was well tolerated and produced some durable radiographic responses at doses of ≤100 ng/ml [29]. However, the potential efficacy of drugs delivered by this technique may be severely constrained by ineffective infusion in many patients.

In conclusion, more fundamental information on the nature of these cancers in terms of molecular biology is being addressed through the auspices of a European project, resulting in the creation of a malignant glioma database and tissue bank and through ongoing research activities being undertaken by specified groups [1, 4].

However, at present it remains unclear how best to integrate new discoveries in glioma molecular biology into clinical practice [12]. Recent studies have supported the concept that malignant gliomas might to be seen as an orchestration of cross-talk between cancer cells, their micro-environment, the vasculature and cancer stem cells.

Furthermore, the oncogenetic process in such tumours is driven by several signalling pathways that are differentially activated or silenced with both parallel and converging complex interactions. Therefore, it is difficult to identify prevalent targets that act as key promoters of oncogenesis that can be successfully addressed by novel agents [26]. A better strategy may be to identify common molecular abnormalities that are targets of more universally applicable therapies. Thus, novel successes in the fight against certain devastating cancers might be achieved by the combination of pro-autophagic drugs such as temozolomide with mTOR, class I PI3-K or Akt inhibitors or with endoplasmic reticulum stress inhibitors or anti-migratory drugs as adjuvant chemotherapies [14, 19]. It is probable that the improved treatment of these invasive brain tumours will depend on the blending of cocktails of targeted agents that are tailored for individual patients.

Finally, it is to be further hoped that novel therapies derived from better cellular and molecular understanding of glial tumourigenesis and of the interaction between these cancers and their micro-environment, and advances in non-invasive diagnosis including the visualisation of tumour tissue by fluorescent methods [35] and intra-operative monitoring permitting more radical tumour resection and adjuvant treatment, will significantly improve the clinical outcome of these devastating lesions.

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