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Management of Malignant Glioma – Quo Vadis?

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After years of disappointment and nihilism, treatment of glioblastoma has emerged as a worthwhile and rewarding endeavor. This does not mean patients suffering from malignant primary brain tumors are all of a sudden cured or carry an excellent prognosis. However, persistent research, rational development of new agents, systematic clinical investigation and multimodality treatments have led to tangible improvements in outcome and quality of life of patients, better understanding of the disease(s) and renewed interest in further investigation. Temozolomide (TMZ) has emerged from mastering of chemistry and rational drug design as a modestly active agent against recurrent glioma (reviewed in [1]). Subsequent academic investigation developed alternative administration schedules, notably prolonged continuous TMZ exposure allowing for higher dose intensity and potentially increased efficacy by exhausting the endogenous methyl-guanine methyl-transferase (MGMT) reservoir [2]. As first line treatment of glioblastoma, concomitant administration of TMZ and radiotherapy followed by up to 6 cycles of maintenance TMZ (TMZ/RT → TMZ) have led to prolonged survival as repeatedly shown in phase II and phase III clinical trials [3–5]. Importantly, correlative science has demonstrated that *MGMT* gene promoter methylation status is an important predictive marker for outcome [6, 7].

In this issue of ONKOLOGIE, Yaman and colleagues report on their experience of treating patients with glioblastoma and anaplastic astrocytoma with the current standard of care of TMZ/RT followed by TMZ as a first line of treatment [8]. They retrospectively analyzed the outcome of 64 patients with glioblastoma or anaplastic astrocytoma treated between 2005 and 2007. They define the eligibility criteria, although they do not provide assurance that all patients diagnosed during that time were evaluated, and data are presented clearly. Their publication confirms the wide applicability of the established treatment in the setting of routine practice and thus provides evidence that the outcomes measured in the setting of clinical trials can indeed be reproduced in real life. Similarly, the side effects of this treatment regimen remain mild to moderate. Yaman et al. report improved progression free survival and overall survival for their glioblastoma population compared to those published in the phase III trial, even though cross-trial comparisons have to be cautioned, as well as comparisons between a phase III trial and a single-arm retrospective review [4]. The authors speculate about reasons for improved outcome, notably prolonged administration of TMZ for more than 6 cycles in two thirds of the patients while unfortunately ignoring established clinical prognostic factors and omitting to analyze molecular markers [9, 10]. For instance, the patient population reported here is almost 10 years younger than in the pivotal TMZ trials. In this study almost 95% of the patients had debulking surgery (compared to 80% in other reports) and the percentage of patients requiring steroids for symptom control was also much lower. No effort was made to analyze MGMT, the strongest variable of outcome in previous reports. Nevertheless, the authors raise a number of important questions:

The role of intensified TMZ administration schedules will be answered soon by the ongoing RTOG0525/EORTC 26052–22053 Intergroup trial. The accrual goal of over 1,100 patients will be reached in June 2008. In this protocol patients are stratified by MGMT promoter methylation status, and then randomized after the end of TMZ/RT to either standard dose (daily × 5/28 days) maintenance therapy versus dose-dense (21/28 days). It will also allow confirming the predictive value of MGMT status within a prospective trial.

Controversy remains about the optimal duration of TMZ treatment. In the randomized EORTC/NCIC (European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada) landmark phase III trial [4], and in the preceding phase II trial [3], temozolomide was administered for a total of maximum 6 adjuvant (maintenance) cycles

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after the end of concomitant TMZ/RT, similar to adjuvant chemotherapy in colon or breast cancer. However, in contrast to other solid tumors, in malignant glioma residual measurable macroscopic disease often remains, which is for many physicians a reason to pursue therapy until progression. In our experience and in analogy with other solid tumors, there is little if any evidence suggesting improved outcome with prolonged therapy. Radiological response in the brain is often delayed and may be seen even months after discontinuation of chemotherapy.

The accurate assessment of progression in primary brain tumor patients is a challenge. Tumor response with increased necrosis and associated inflammation may give rise to increased contrast uptake and may lead to false interpretation as progressive disease (reviewed in [11, 12]). In one series of patients undergoing second surgery for presumed progression after TMZ/RT, no viable tumor tissue was found in close to 50% of the patients [13]. In a recent report, Brandes and coworkers demonstrated that the so-called 'pseudoprogression' is most frequently associated with tumors with a methylated *MGMT* gene promoter, thus tumors most likely to respond to TMZ chemotherapy [14]. Although we do not routinely assess the MGMT status outside of clinical trials in the absence of a treatment alternative, in cases of suspected pseudoprogression it may be helpful for deciding whether to pursue the TMZ chemotherapy a little longer or whether to change for a salvage chemotherapy regimen [15].

Only little data is available on chemotherapy after failure of first line TMZ/RT → TMZ. Unfortunately the current report does not indicate what regimens have been used after progression. Temozolomide for recurrent disease has been approved before this drug was used in the initial management of glioblastoma. After an exposure-free interval re-treatment with TMZ with either the standard or an alternative regimen may be of value. The nitrosoureas (carmustine or lomustine) have shown some efficacy in recurrent disease and have been used as control arm in a recent randomized trial [16]. We have used irinotecan as a single agent for several years. Most recently, reports on the use of bevacizumab with irinotecan have received attention [17]. However, the only randomized (phase II) trial compared bevacizumab with bevacizumab plus irinotecan and showed prolonged time to progression with the combination, but no difference in overall survival (8–9 months) [18]. As the experimental agent was included in both arms, no definitive conclusion on its efficacy can be drawn. In our daily practice we use bevacizumab in association with irinotecan in patients with a mass effect and significant edema. Although we only use 5 mg/kg of bevacizumab (compared to 10 mg/kg in the US trials), we observed rapid edema reduction allowing for rapid taper of the corticosteroids and improvement of the patients' condition.

One of the merits of establishing TMZ as an active agent was stopping to lump together histologic entities with distinct prognoses, such as glioblastomas and anaplastic gliomas. Systematic investigation of grade 3 gliomas including molecular markers have allowed to identify anaplastic oligodendroglioma with chromosomal loss on chromosomes 1p and 19q (loss of heterozygosity (LOH) 1p/19q, recently identified as a translocation [19, 20]) as a distinct pathologic entity with a protracted natural history independent of treatment. In parallel, randomized trials in anaplastic oligoastrocytoma and oligodendroglioma, – an entity thought to be particularly chemosensitive – have failed to demonstrate an improved survival with (neo-) adjuvant PCV- (procarbazine, lomustine, vincristine) chemotherapy, despite prolonged progression-free survival [21, 22]. In an ongoing EORTC Intergroup trial (CATNON trial) patients without LOH 1p/19q will be randomized to either standard radiotherapy alone, or RT and concomitant TMZ (RT/TMZ), or RT followed by TMZ (RT → TMZ) or the full combo of TMZ/RT → TMZ. This ambitious trial should also allow to estimating the relative contribution of the concomitant TMZ administration during RT, or during the maintenance phase.

The renewed interest in developing novel therapies in malignant glioma is also reflected in the number of large clinical trials being developed for this disease. To our knowledge, no less then 4 large randomized trials are in preparation or about to start, most advanced are trials investigating new promising anti-angiogenic agents, such as bevacizumab or the integrin-inhibitor cilengitide, added to the TMZ/RT combination [23, 24]. One lesson learned from the TMZ experience is that a new agent should be given a fair chance for demonstrating its efficacy, thus administration early in the disease course is needed. Furthermore, efficacy and notably response rates in recurrent disease may not be predictive for the efficacy of a new agent for treatment of brain tumors – the response rate for TMZ in recurrent glioblastoma was only 5% and 8%, respectively in 2 pivotal trials –. And lastly, the concomitant administration of chemotherapy with radiotherapy may be needed to truly impact on the disease [25].

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