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RS and MW have served on advisory boards for Merck KGaA, Roche and Schering-Plough. RS and MW are the principal investigators of phase II and phase III trials investigating cilengitide in malignant glioma.

For decades alkylating agent chemotherapy for malignant glioma was considered of little benefit and its use varied greatly. In 1999 temozolomide (TMZ) was approved in the United States based on a 35% radiological response rate in recurrent anaplastic astrocytoma, however, in recurrent glioblastoma the objective response rates were well below 10%. The primary trial endpoint of the percentage of patients being progression-free at 6 months (PFS6) was rejected by the Food and Drug Administration (FDA). Full approval was obtained only when a large randomized phase III trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) demonstrated a reduction of the risk of death of 37%, translating in 2-year survival rates of 27% for concomitant and adjuvant chemoradiotherapy (TMZ/RT → TMZ) versus 10% with initial radiotherapy alone. Nevertheless, the majority of patients still die within 2 years, and novel treatments are urgently needed. This has also been recognized by the pharmaceutical industry, and novel treatments are being developed and tested early on in glioma patients.

Glioblastoma are highly angiogenic tumors, and inhibiting or modulating angiogenesis and tumor vasculature is a logical target. At least four drugs are aiming to make their way into the clinic: Bevacizumab, a monoclonal antibody binding circulating vascular endothelial growth factor (VEGF), and cediranib, a tyrosine kinase inhibitor for the VEGF receptor (VEGFR) are direct inhibitors of the VEGF pathway. Enzastaurin, a protein kinase C inhibitor, is indirectly also inhibiting the VEGF pathway. Finally, cilengitide is a first-in-class inhibitor of integrins alphavb3 and alphavb5 which are specifically expressed on tumor-associated microvasculature, but also on glioblastoma cells. Blocking these integrins will inhibit angiogenesis, tumor cell attachment and migration.

Different strategies have been chosen to seek regulatory approval. AstraZeneca is conducting a large phase III trial of cediranib as a single agent or in combination with lomustine versus lomustine alone in recurrent glioblastoma. Bevacizumab has already obtained FDA approval based on two small phase II studies showing high radiological response rates in recurrent glioblastoma. Enzastaurin has failed to demonstrate significant single agent activity in a phase III trial in recurrent glioblastoma (and provided us with current efficacy data of lomustine in this setting), and this drug is now being investigated in combination with radiotherapy or TMZ/RT in newly diagnosed disease. Cilengitide has consistently shown responses, some of which were durable, in patients with recurrent glioma in phase I and phase II studies, as well as encouraging activity in uncontrolled phase II studies in patients with newly diagnosed

glioblastoma. A pivotal large randomized phase III study was launched in 2008 for patients with newly diagnosed glioblastoma in combination with standard TMZ/RT → TMZ.

The clinical experience with these drugs has tought us several lessons:

First, our classical response criteria defined by Macdonald and colleagues almost 20 years ago seem no longer helpful if we are to assess the effects of antiangiogenic agents based on neuroimaging. Recognizing these limitations, an international working group has been formed revisiting response assessment and endpoints for clinical trials in brain tumors.

While TMZ has almost failed to meet criteria for drug approval because of low response rates in recurrent glioblastoma, the drug when given early in the disease course and concomitant to radiotherapy demonstrated meaningful activity. Enzastaurin despite promising phase I and II data failed to demonstrate measurable single agent activity when given to patients with recurrent glioblastoma. Thus the fastest way to the market may not always be the quickest, and testing new agents in the upfront setting may be advantageous. However, this requires complex trial designs and combination with other chemotherapy and with radiotherapy, with the potential risk of unexpected toxicity.

For some of the targeted agents no single agent activity may be demonstrated, however, in combination the drug may still be active and very useful. The three-arm design of the cediranib trial may have been based on the unfortunate experience with enzastaurin. This large randomized phase III trial is recruiting very fast and initial results are expected for ASCO in 2010.

A different strategy was adopted for cilengitide. Although some responses were seen as a single agent in recurrent glioma, development focused – based on theoretical and preclinical considerations – on combination with radiation and chemotherapy. Subsequently a phase III trial was launched specifically in glioblastoma with *MGMT* promoter methylation, a subgroup of tumors previously identified to be most responsive to alkylating agent chemotherapy. And a robust primary endpoint of overall survival was chosen.

For bevacizumab no formal drug development in glioblastoma had been planned. However, small uncontrolled phase II trials suggested dramatic radiological tumor responses, a decrease in steroid requirement and often improvement in quality of life. Toxicity, in particular hemorrhages and thrombo-embolic events, were in an acceptable range. Based on these findings, and following a highly emotional debate of the Oncology Drug Advisory Committee (ODAC), the FDA granted approval for the treatment of recurrent glioma. Nevertheless, neither the optimal dose nor the frequency of administration or its use as a single agent or in

combination with a cytotoxic agent have been established, and are unlikely to be established in the near future. Despite its undisputed usefulness in some clinical situations, the drug may have significant disadvantages in the treatment of glioma :

i) Prolonged administration will induce dose-dependent hypertension, presumably with an increased risk for intracranial hemorrhage.

ii) Recent clinical experience suggest a modification in the tumor phenotype upon long-term treatment with bevacizumab, with diffuse infiltration of large areas of the brain and recurrence at distant sites of the CNS seen more commonly

iii) Discontinuation of bevacizumab may induce a rebound with rapid increase in contrast-enhancement and edema; thus, patients once started on bevacizumab may need to continue indefinitely.

iv) Finally, the early use of bevacizumab makes the clinical investigation of other novel compounds at progression or recurrence difficult. The rebound phenomenon may occur as late as 6-8 weeks after the last dose due to the long biological half-live of the monoclonal antibody. Thus it would require to withholding antitumor treamtent to a progressing patient for 2 months before a salvage therapy could be considered in the context of a clinical trial. Furthermore, to date all investigated drugs given after bevacizumab failure either alone or in combination failed to demostrate any responses.

v) The approval of bevacizumab based on insufficient data also set a regulatory precedent. If a drug is approved (too) early in its development process, and without the conduct of appropriate clinical trials, it will be difficult to ever determine its optimal use. Furthermore, it sets an example for potential competitors to design experiments in a fashion that a presumably active agent cannot fail, e.g., as for bevacizumab using the experimental agent in both arms of an underpowered randomized trial, rather than going trough the effort and expense of an appropriate phase III clinical trial.

Many of the above-mentioned controversies have not been resolved at this point in time, In constrast to a decade ago when the first novel agent for brain tumors entered clinical investigation, we now witness a wave of novel antiangiogenic, vaculature-modifying agents and targeted agents. Careful utilization of research resources, smart and innovative trial

design and international collaboration is required to translate this most fruitful period in neurooncology to the benefit of our patients.

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