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Angiogenesis inhibition in high grade glioma

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Summary

In **chapter 1** we introduce Glioblastoma multiforme (GBM) and describe the development of current treatment modalities. GBM is a devastating disease with a dismal prognosis, even under highest standard of treatment median overall survival is only 14 months. In the Netherlands, every year approximately 800 new patients are diagnosed with this malignancy.

First, we discuss different types of brain tumors. The possible implications of the cancer stem cell (CSC) paradigm are discussed; furthermore we highlight the interaction with the tumor environment, especially the tumor endothelial cells. Treatment modalities are placed in a historical perspective and most up-to-date regimens are pointed out for primary GBM and recurrent tumors. Special attention is paid to tumor angiogenesis and inhibitors of angiogenesis. Treatment options and side effects are discussed. Next, the combination of angiogenesis inhibition and irradiation is discussed, with the possible pitfalls. Finally, imaging modalities are presented.

In vitro experiments

In **chapter 2** we investigate an improved *in vitro* model system for interaction between GBM and tumor-microenvironment, where not only interaction of tumor cells and tumor microvascular endothelial cells (tmVECs) from the same species can be examined, but also of cells derived from within the same tumor. This system underscores the differences between tumor microvasculature and the more commonly used human vascular endothelial cells (HUVECs). Furthermore it reveals that direct contact between endothelial cells and CSCs is needed, as is not observed for commonly used GBM cell lines as U87. For CSCs probably factors that require a close proximity between both cell types could mediate the observed effects.

In vivo experiments

In **chapter 3** radiation treatment in an intracerebral tumor mouse model is explored. External beam irradiation at clinical relevant high doses is technically impossible to deliver to the brain without inflicting lethal damage to healthy tissues, due to dimensions of the head of smaller rodents than rats. Researchers by-passed this problem by implanting brain tumors in the hind legs of mice, but here microenvironment is dissimilar to brain context. We developed a new tool based on high-dose radiotherapy of orthotopic brain tumors through an implanted stereotactic guide-screw containing ¹²⁵I brachytherapy seeds. Now, irradiation of murine brain tumors is feasible without causing fatal toxicity.

Chapter 4 examines the effects of combined irradiation and angiogenesis inhibition in the intracranial tumor model. We explore safety and efficacy of combined irradiation with DC101, an antibody binding VEGF receptor 2. As expected, untreated mice show highly proliferative, large tumors. DC101 treatment significantly reduced tumor size, but morbidity did not improve. Irradiation induces tumor growth delay and reduced morbidity significantly. Combinational treatment improves local tumor control but, surprisingly,

morbidity and survival are comparable to that of sham-treated animals. Possibly, extracranial side effects caused the higher toxicity. The fact that local irradiation to the brain appears to exacerbate DC101 toxicity is of great concern. Therefore we warn that the combination of radiotherapy with VEGF-R2 blockade can potentiate tumor growth delay but may inadvertently lead to unexpected morbidity.

In **chapter 5** we investigate whether irradiation synergizes with the anti-VEGF aptamer pegaptanib and explore the impact of this combined treatment on tumor invasion into the normal brain. Interestingly, anti-angiogenic treatment inhibits local tumor growth, but does not inhibit tumor invasion, in agreement with angiogenesis-independent tumor infiltration. We find that combined irradiation of the tumor plus surrounding normal brain not only reduces tumor bulk growth and increases PFS, but also suppresses invasive growth. Whole brain irradiation with generous boosting fields could theoretically attack all invasive tumor components. To minimize late radiation toxicity, better imaging techniques (like MRSI) are required to visualize the invasive tumor components.

Clinical experiments

Chapter 6 shows that combined irradiation with angiogenesis inhibition should be administered with caution, as pointed out by this case report on combined irradiation and sorafenib, a small molecule with angiogenesis inhibiting activity which acts by blocking the signaling through vascular endothelial growth factor (VEGF) receptor and the platelet-derived growth factor receptor. A patient receiving sorafenib developed a lumbar metastasis that required irradiation. She died of complications in the bowel—the area directly targeted by irradiation. Possibly the 2-day gap between the end of sorafenib treatment and the start of radiotherapy (1 x 8Gy) was too short. As the *in vivo* study on DC101 also suggests, this case provides evidence for potential oversensitization of normal tissue by VEGFR-2 inhibition.

Chapter 7 shows that anti-angiogenic treatment is well feasible in recurrent HGG patients, with low toxicity. We report the results of a study to the combined treatment of 3-weekly bevacizumab and temozolomide (TMZ) in a daily dose regimen, in patients with recurrent HGG. The dynamic MRI parameters K^{trans} and rCBV decreased rapidly during the early phases of treatment as a reflection of changes in vascularisation and vessel permeability but not of anti-tumor activity. In addition, over 50% of patients showed edema reduction and a reduced shift on T1 images. The response data (CE-T1, 20%) in our study are comparable to the ORR reported for single-agent therapy but they are considerably lower than the reported response rates up to 57% in previous studies for bevacizumab combined with irinotecan. The median PFS6 (17.4 weeks), the median PFS (13.9 weeks) and median survival (17.1 weeks) were considerably lower compared to most other studies with bevacizumab containing regimens. Patient selection may be an explanation for our inferior results. Additional factors may be the kind of chemotherapy combined with bevacizumab, and the

schedule of bevacizumab administration. An alternative explanation for the negative results in this study may be that temozolomide actually negates the benefits of bevacizumab.

Chapter 8 discusses the potential drawbacks of inhibition of angiogenesis in GBM. GBM can be roughly separated into an angiogenic component, and an invasive or migratory component. Although this latter component seems inert to anti-angiogenic therapy, it is of major importance for disease progression and survival. Clinical symptoms are tempered by anti-angiogenic treatment, but tumor invasion continues e.g. by co-option of pre-existing vasculature. Unfortunately, anti-angiogenic treatment interferes with MR imaging too, making it even harder to define tumor margins. Moreover, while treatment of other tumor types may be improved by combining chemotherapy with anti-angiogenic drugs, inhibiting angiogenesis in GBM may antagonize the efficacy of chemotherapeutic drugs by normalizing the blood-brain barrier function. Although angiogenesis inhibition is of considerable value for symptom reduction in GBM patients, lack of proof of a true anti-tumor effect raises concerns about the place of this type of therapy in the treatment of GBM.

Chapter 9 summarizes overall results and discusses future perspectives. The reduced survival time found in the recurrent HGG study is discussed in the light of the pre-clinical finding that anti-angiogenic treatment not only reduces vessel permeability but may also have potential drawbacks. Placebo-controlled randomized trials are necessary to rule out patient selection bias and treatment bias.

In the coming years, clinically available biomarkers for GBM and further analysis of gene-expression patterns and proteomics will facilitate the development of tests that will identify those patients that will benefit from specific treatments. Future research should focus on preventing invasive tumor growth, on improving irradiation modalities and on developing modifiers of the blood brain barrier to increase penetration of chemotherapy into the brain.