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Angiogenesis inhibition in high grade glioma

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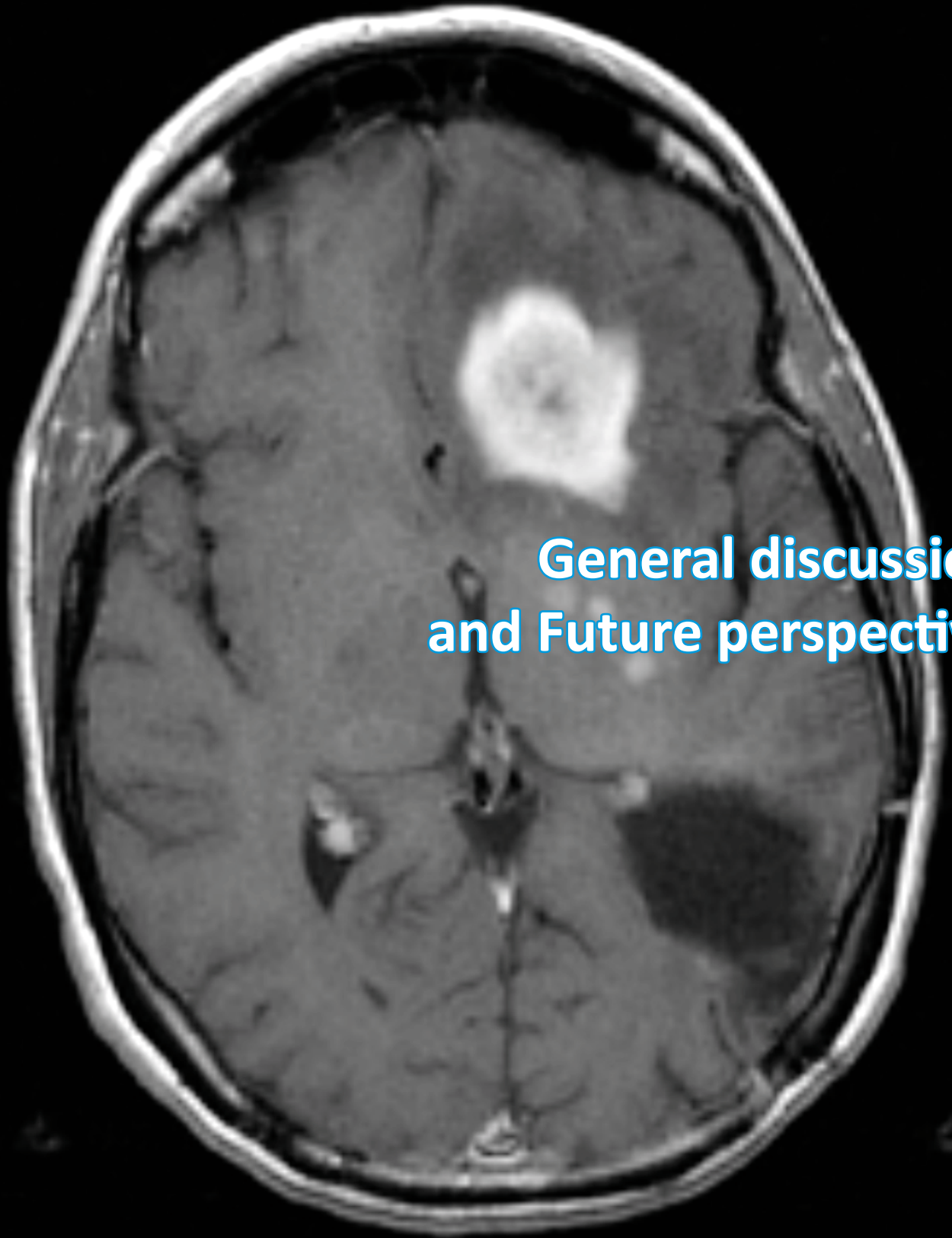
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Chapter 9.



**General discussion
and Future perspective**

General Discussion

Glioblastoma multiforme (GBM, or High Grade Glioma, HGG) is a devastating disease with a dismal prognosis even under highest standard of care. Every year in the Netherlands approximately 800 new patients are presented. Current treatment consists of surgical resection followed by irradiation combined with temozolomide. For recurrent disease, no standard treatment is established.

Hanahan and Weinberg defined six hallmarks of cancer: self-sufficiency in growth signals, insensitivity to growth-inhibitory (anti-growth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (Hanahan and Weinberg, 2000). One of the pivotal hallmarks of GBM, i.e. displaying a high vascularisation, made treatment with angiogenesis inhibitors an attractive option.

Not only pruning of abundant tumor vasculature is of interest for deprivation of tumor cells; angiogenesis inhibitors will probably affect also the functioning of the niche for GBM CSCs, which is thought to consist of endothelial cells. In our *in vitro* co-culture model the necessity for direct cell-cell contact between CSCs and tumor micro-vascular endothelial cells (tMVECs) was shown (**chapter 2**). The complex factors that promote cell growth and therapy-resistance should be further examined. Special attention should be paid to the influence of the niche on radiation resistance, as irradiation is the pivotal treatment for GBM. Interaction between CSCs and their niche is partially hosted by short range acting members of the Sonic Hedgehog family, membrane bound receptors and ligands of the notch-family, both of which have already been shown to stimulate the growth of brain tumors (Becher et al., 2008; Fan et al., 2006; Rudin et al., 2009; Von Hoff et al., 2009; Yauch et al., 2008; Dlugosz and Talpaz, 2009).

In vivo studies still are the cornerstone of translational research. We showed that local irradiation to the brain exacerbates toxicity of VEGFR-2 blocking agents (**chapter 4**), what is of great concern. Furthermore, the anti-tumor effects of local VEGF inhibitors were partially circumvented by the formation of invasive tumor satellites, while local tumor control was present (**chapter 5**). Here, combined irradiation was effective in slowing down proliferation of these invasive tumor components. Therefore, whole brain irradiation with generous boosting fields would theoretically be best to hit invasive tumor components, for primary and recurrent HGG.

The benefits of re-irradiation were shown in recurrent HGG using hypofractionated stereotactic radiotherapy (hFSRT) after primary high-dose irradiation combined with chemotherapy (Fokas et al., 2009). After hFSRT with cumulative doses > 30Gy, the median survival was 9 months, and the 1-year progression-free survival (PFS) amounted to 22%. In addition, to minimize late radiation toxicity, improved imaging techniques (e.g. MRSI) will be required to better visualize these invasive tumor components and enable more precise treatment with irradiation (Park et al., 2007; Stadlbauer et al., 2008). Illustrative is the treatment planning by PET(SPECT)/CT MRI fusion with higher efficacy of defining gross tumor volume for fractionated stereotactic

radiotherapy (6 x 5 Gy in 6 days) leading to a median patient survival of 9 months (Grosu et al., 2005)

How precarious combined irradiation and angiogenesis inhibition in the clinical setting can be is illustrated by a case report (**chapter 6**) on emergency irradiation for a patient being treated with sorafenib (Peters et al., 2008). This case provides evidence for potential oversensitization of normal tissue by sorafenib, possibly by discontinuing sorafenib two days prior to irradiation leading to upregulation of endothelial activity during irradiation, due to increased levels of VEGF that are induced by anti-VEGFR treatment (Bocci et al., 2004). Interestingly, *in vivo* models showed that sequential administration of irradiation following anti-angiogenic treatment (or the other way around) led to a higher anti-tumor effect than when administered in a concurrent setting (Williams et al., 2004; Ning et al., 2002). More research is warranted on sequence and timing of anti-angiogenic treatment and the interplay with combined modalities to maximize therapeutic effects.

In recurrent HGG patients not receiving irradiation, we showed that anti-angiogenic treatment combined with TMZ is well feasible, with low toxicity profiles (**chapter 7**). The response data in our study were considerably lower than the reported response rates up from 28% to 57% in previous studies for both bevacizumab as single agent therapy and combined with irinotecan (Vredenburgh et al., 2007; Friedman et al., 2009). An explanation may be that we administered bevacizumab every three weeks instead of every two weeks in the other studies. Although the three weekly administration of bevacizumab is common practice in other solid malignancies, the kind of schedule and chemotherapy used in bevacizumab containing regimens seems to be important for outcome (Raizer et al., 2009). An alternative explanation for the negative results in this study may be that temozolomide actually negates the benefits of bevacizumab.

Additionally, we quantified K^{trans} as measure for permeability and/or blood flow, and rCBV as measure for tumor blood volume, at baseline and at various time-points during treatment and at relapse. All these parameters were decreased considerably at day 3 and day 21 compared to baseline, supporting the evidence that bevacizumab rapidly affects permeability and blood flow and is active 3 weeks after infusion. Nevertheless, we conclude that determination of the time to progression based on changes of enhancing tumor areas or volumes is difficult and not useful for evaluating antiangiogenic therapy in tumors behind a BBB (**chapter 8**).

The resulting reduced survival time further supports the pre-clinical finding that anti-angiogenic treatment not only reduces vessel permeability for contrast enhancing agents but may also reduce the activity of TMZ by limiting drug penetration (Claes et al., 2008). Therefore our study again demonstrates that placebo-controlled randomized trials are necessary to rule out patient selection bias and treatment bias.

Future Perspective

This thesis covers the first steps towards a clinical implementation of combined VEGF inhibition with irradiation, to further improve survival of glioma patients. Further steps are needed to define the optimal role of angiogenesis inhibition in the treatment of GBM, next to development of new additive treatments and new strategies to monitor treatment efficacy. Several interesting additive strategies are discussed below.

Now individualized medicine comes within reach, the identification of predictive and prognostic markers for treatment response will become more important, (van den Bent and Kros, 2007). Individualized medicine is completely depended on reliable biomarkers, for example as read-out for patient response of angiogenesis inhibitors, as MR imaging is thoroughly biased by these compounds. Examples of clinical available biomarkers for GBM are 1p/19q loss, MGMT methylation status, EGFR amplification. 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 (Diks and Peppelenbosch, 2004; van't Veer and Bernards, 2008).

Individualized cancer treatment has become a realistic option for several malignancies since the characterization of molecular markers for response / disease outcome, and the discovery of specific therapeutic targets, mostly aberrant functioning signaling proteins, for tailor made therapy.

Predictive factors of treatment response

1p 19q status

Molecular tumor characterization can strongly predict patient survival, as is illustrated by the testing of loss of chromosomal arms 1p and 19q. Brain tumor cells that have lost both arms as detected with fluorescent in situ hybridization (FISH) not only grow slower, these patients also respond better to DNA damaging therapies (Smith et al., 2000). This is robustly the case for oligodendroglioma, the glial brain tumor that histologically have the appearance of oligodendrocytes, the myelin forming cells in the brain. Nevertheless, for histological-proven glioblastoma, 1p 19q status seems not to influence outcome in a positive way, these patients even tend to survive shorter (Smith et al., 2000; Kaneshiro et al., 2009). Histological distinction between oligodendroglioma and GBM is therefore important prior to determining 1p 19q status.

MGMT status

The large randomized controlled clinical trial of Stupp et al (Stupp et al., 2005) revealed that promoter methylation of the O6-methylguanine-methyltransferase gene (MGMT) was the strongest predictive marker for survival in the group of patients treated with temozolomide and radiotherapy compared to radiotherapy alone (Hegi et al., 2005). The MGMT gene is located on chromosome 10 and encodes MGMT, a DNA repair protein that is considered to counteract the effect of alkylating chemotherapy by removing methyl groups from the O6-position of guanine (Jacinto and Esteller, 2007). Inhibition of MGMT protein expression follows from

transcriptional silencing as result of epigenetic MGMT promoter methylation at cytosine guanine dinucleotide clusters, the so called CpG islands. Low expression of MGMT results in an improved patient survival. The relevance of MGMT as potential prognostic or predictive factor in malignant glioma patients is supported by a number of independent studies (Dunn et al., 2009; Stupp et al., 2009). Therefore, there is strong interest in incorporating testing of MGMT promoter methylation status into clinical GBM trials (Preusser, 2009).

Concerning the day-to-day clinical practice, MGMT assessment is not yet part of the routine diagnostic work-up of GBM specimens, because the current standard therapy strategy for newly diagnosed GBM is regardless of MGMT status. Furthermore there is a lack of data to base recommendations on for a specific method or protocol for MGMT status testing (Preusser, 2009; Stupp et al., 2009).

EGFR status

Amplification of the EGFR gene and overexpression of the EGFR protein occurs in 40% of primary GBM and is therefore the most common alteration (Libermann et al., 1984; Wong et al., 1992). The most common mutation of EGFR is named EGFRvIII (Gan et al., 2009). This mutation is not observed in normal tissue, but occurs in 20 to 30% of unselected GBM patients. A loss of exons 2 to 7 of the EGFR gene results in an in-frame deletion of 267 amino acids in the formed EGF receptor. This receptor is unable to bind ligands, but is actively signaling (Prigent et al., 1996).

Targeted therapy against EGFR or specifically against EGFRvIII is explored to stop tumor growth. Retrospective analyses pointed out that co-expression of EGFRvIII and wild-type PTEN (phosphatase and tensin homologue deleted in chromosome 10) is a predictor of response to tyrosine kinase inhibitors (TKI) in HGG patients (Brewer et al., 2005). In particular tyrosine kinase inhibitors gefitinib and erlotinib are already being tested extensively in clinical trials, with mixed results (Gan et al., 2009). Combined strategies against downstream pathways PI3-kinase, mTOR, or G1cyclins may further enhance activity of EGFRvIII blockers (Mellinghoff et al., 2005).

A functional PTEN is necessary to prevent PIP3 levels to accumulate while downstream signaling continues despite upstream EGFR blockade. Downstream from PTEN and PI3K is mTOR. Gefitinib and erlotinib have been combined with the mTOR inhibitors, temsirolimus and everolimus, with modest effects on progression-free survival (Reardon et al., 2006; Doherty et al., 2006). Administering a dual PI3K and mTOR inhibitor with erlotinib (thus "triple blockade") demonstrated more effective growth arrest than any two targeted therapies in combination (Fan et al., 2007).

Oncogene or pathway addiction is, in contrast to other tumors (e.g. myelogenous leukemia (Druker et al., 2001) or gastrointestinal stromal tumors (Demetri et al., 2002)) not detected in GBM, where genetic heterogeneity and existence of multiple parallel or compensatory pathways result in treatment failures. Recently, full genome sequencing revealed enormous numbers of mutations in individual malignancies and extensive heterogeneity between individual patients

(Wood et al., 2007; Mardis et al., 2009). Most likely, this will have consequences for the principle of oncogene addiction and predictive assays for the efficacy of small molecule inhibitors and antibodies.

Serum biomarkers

There are no biomarkers for monitoring response to angiogenesis inhibitors in brain tumors, in contrast to pre-treatment measurement of ADC by dynamic MRI (Pope et al., 2009). The various imaging methods based on contrast enhancement are difficult to use as response monitors because contrast enhancement is hindered by anti-VEGF treatment.

Recently, serum biomarkers are being tested for glioma, e.g. increased levels of methylated tumor-specific DNA in plasma (Weaver et al., 2006). Also, GFAP serum levels are found to be elevated in GBM patients prior to surgery, and therefore this level is a potential biomarker for treatment response monitoring (Jung et al., 2007). As a pilot study, we measured GFAP plasma levels in 12 recurrent HGG patients before start and during treatment with bevacizumab and TMZ. Seven patients did not have detectable GFAP serum levels before and during treatment. Although sample size was small, in 5 remaining patients we observed a trend in GFAP plasma decrease under bevacizumab plus TMZ treatment from 0.28 ug/L to 0.12 ug/L during treatment ($p=0.06$) (*unpublished data*). Additional sampling of hypoxia marker Ca-IX in plasma detected baseline levels in 9 patients, that increased by anti-angiogenic treatment (baseline 29.1 pg/L to 50.1 pg/L during treatment; $p=0.10$). We may speculate that decreased GFAP plasma levels reflect restored (lowered) tumor vessel permeability for larger debris particles, but it could also mean that anti-tumor activity of bevacizumab and TMZ decreased tumor load and did increase hypoxia. This pilot may indicate a possible role for plasma GFAP and CA-IX as treatment biomarker, results from a larger cohort are needed.

A promising field of interest is the discovery of microvesicles providing diagnostic information (Skog et al., 2008; Al-Nedawi et al., 2009). This technique could partly replace the need for neurosurgical biopsies. For example, Skog et al. detected tumor-specific EGFRvIII microvesicles in serum from 7 out of 25 glioblastoma patients, facilitating treatment selection.

Anti-angiogenic drugs enable neo-adjuvant chemoradiation

Currently, most GBM patients will have to undergo surgery within one or two weeks after initial diagnosis, to prevent cerebral edema causing major neurological problems. Angiogenesis inhibition showed to treat brain edema effectively, even better than corticosteroids and with less side effects (Batchelor et al., 2007; Green et al., 2007). This could implicate that it is feasible to postpone neurosurgery and to start directly with neo-adjuvant chemo-irradiation treatment, containing an angiogenesis inhibitor e.g. bevacizumab or AZD2171. Safety of this combination is not yet established. Therefore, in 2009 we performed a clinical trial in primary GBM patients, where surgery or biopsy was followed by irradiation and TMZ plus 2 weekly bevacizumab during

irradiation (BERTES trial, NTR1148). Preliminary safety data are promising but we are also interested in overall survival and recurrence patterns in these patients, as a more invasive phenotype may arise (Lai et al., 2008). In a comparable study in 70 primary GBM patients the progression free survival improved, but not the overall survival (Lai et al, abstract 297 SNO meeting 23 October 2009).

Neo-adjuvant chemotherapy successfully downstaged other tumor types, e.g. it improved resectability and locoregional control in locally advanced breast cancer, esophageal cancer, locally advanced colorectal cancer, resectable non-small cell lung cancer stage III and locally advanced cervix carcinoma (Kapiteijn et al., 2001; Liao et al., 2004; Bosset et al., 2005; Cunningham et al., 2006; Sebag-Montefiore, 2006; Hou et al., 2007; Uy et al., 2007; Waljee and Newman, 2007; Rosenberg, 2007). However, in those studies neo-adjuvant treatment did not unambiguously result in an improved progression free survival and overall survival.

Eighteen initially inoperable recurrent HGG patients received neo-adjuvant chemotherapy (high dose methotrexate and 5-fluorouracil) to debulk tumor mass and improve patient performance status. Post-treatment, 5 re-operable patients had significantly longer PFS than 13 not re-operated patients (Boiardi et al., 1992). Neo-adjuvant chemoradiation of HGG has also been attempted previously, in 10 patients with a hypervascular, high-grade astrocytoma (Seiler et al., 1979). This regimen tended to reduce tumor vascularization, thereby facilitating more straightforward surgery without compromising hemostasis or wound healing. Nevertheless, overall survival did not improve.

In conclusion, there is a strong rationale for exploring safety and efficacy of neo-adjuvant chemo-radiotherapy combined with angiogenesis inhibition, e.g. AZD2171 or bevacizumab, as first-line treatment of GBM patients. However, the invasive character of GBM is the Achilles' heel of all anti-GBM treatments and should be taken into account.

Targeting invasion

As this thesis points out, invasion is a pivotal feature of GBM that is not targeted by mono-treatment with angiogenesis inhibitors. Promising regimens that interfere with invasion come within the reach. Several strategies against invasion have already been tested in pre-clinical models. Glioma cells first have to detach from the growing tumor mass and the extracellular matrix (ECM) to invade surrounding tissue (Nakada et al., 2007). Stimulation of matrix metalloproteinase (MMP) transcription by glioma cells leads to enhanced invasion. Drugs blocking MMP show down-regulated invasion in vivo (Koutroulis et al., 2008). Nevertheless, recent clinical phase II studies do not show survival advantage for recurrent GBM patients treated with MMP inhibitor marimastat (Groves et al., 2002; Levin et al., 2006). Additionally implicated for invasion and migration are integrins, transmembrane receptors that bind multiple extracellular matrix ligands. Several clinical phase I - II trials have been conducted with drugs targeting integrin interaction, e.g. EMD121974 (Cilengitide) (Nabors et al., 2007; Reardon et al., 2008). This drug was well tolerated by patients, partial responses were noted and larger studies are commenced now.

Inhibition of the PI3K/AKT pathway by mTOR inhibitors leads to decreased migration and increased sensitivity for apoptosis, in pre-clinical trials (Fasolo and Sessa, 2008). These compounds are now also being tested in the clinic, but first results are disappointing (Chang et al., 2005; Cloughesy et al., 2008).

Numerous 'new kids on the block' are brought to clinical studies and need to prove their alleged effectiveness in GBM, e.g. proteasome inhibitors (bortezomib, MG132), IKK inhibitors (NSAIDs, sulfasalazine, arsenic trioxide, curcumin), antioxidants (disulfiram, glutathione), GSK3 inhibitors (Lithium), TGF- β inhibitors (AP12009), FAK inhibitors (TAE226, PF-04554878, PF-00562271), c-MET inhibitors (OA-5D5, AMG102, SCH900105, GSK1363089, MP470), EGFR inhibitors (gefitinib, erlotinib, cetuximab), PDGF receptor inhibitors (imatinib) (Drappatz et al., 2009). Although promising *in vitro* and *in vivo*, for all drugs it is of utmost importance that they reach the cancer cells that are located behind the intact blood brain barrier for this is the tumor compartment of GBM that is almost unaffected by nowadays treatments.

Blood brain barrier

Being the best perfused organ of the body, the brain should theoretically be the excellent target for systemic drug delivery. This is not the case because the tissues are fiercely safeguarded by the blood brain barrier (BBB). The BBB is crucial for maintaining homeostasis of the central nervous system, it meticulously controls the composition of its interstitial fluid (de Vries et al., 2006; de Vries et al., 2007). Transport of compounds into and out of the interstitial space is carried out through drug transporters e.g. ATP-binding cassette transporter P-glycoprotein (P-gp; ABCB1) (Juliano and Ling, 1976), and ABC half-transporter Breast Cancer Resistance Protein (BCRP; ABCB2) (Breedveld et al., 2005). This results in a drug penetration that is ten- to hundred-fold reduced, as was shown in knock-out mouse models (Schinkel et al., 1995; Breedveld et al., 2005). Therefore interfering with these transporters seems a promising option.

There are several strategies developed to increase interstitial drug concentrations. They result in a more selective opening of the BBB, use targeted delivery of drug, vector-enhanced delivery, or result in inhibition of the drug transporters. Normal and tumor brain vasculature express several ABC transporters, therefore blocking these transporters, and thereby inhibiting efflux of drugs, could be an effective strategy to increase interstitial concentration (Zhang et al., 2003). A promising inhibitor is elacridar, that partially inhibits ABCB1 in the brain (Kemper et al., 2003).

Drugs that enable temporary opening of the BBB generally act through vaso-activation. Most extensively studied is bradykinin analog RMP-7 (Cereport[®], Labridimil). Nevertheless, a randomized phase II trial in GBM patients treated with combined carboplatin failed to show benefit (Prados et al., 2003).

Targeted delivery of drugs can be employed by using cell-penetrating peptides (e.g. drugs coupled via a spacer to SynB) that are absorbed by endocytosis (Drin et al., 2003; Adenot et al., 2007). In addition, progression is made in vector-enhanced delivery to target glioma tumors, as it

was shown that delivery of oncolytic viruses was enhanced through infected neuronal stem cells (Lamfers et al., 2007; Tyler et al., 2009).

In addition, immunotherapy could be used to target residual treatment resistant tumor cells without damaging healthy surrounding brain tissue (Grauer et al., 2009). Significant progress has been made in recent years both in understanding the mechanisms of immune regulation in the central nervous system (CNS) as well as tumor-induced and host-mediated immunosuppression elicited by gliomas.

The long list of new treatment options indicate that the fight against malignant glioma is not over yet, it only has begun. We showed that one of its hallmarks- i.e. sustained angiogenesis- seems to be under control. Nevertheless this resulted in an escape through another feature, i.e. tissue invasion and metastasis. At least, VEGF inhibition leads to improved quality of life of surviving glioma patients.

The coming years, many new strategies will be tested *in vitro* and *in vivo*, and the most promising will make it to clinical trials. Maybe the breakthrough is enhanced by computational oncology, the sophisticated digital modeling of tumor growth and treatment response (Sottoriva et al., *accepted in Cancer Research*).

History will teach us that most breakthroughs are achieved serendipitously, and as the French scientist Louis Pasteur said: "In the fields of observation chance favors only the prepared mind". One day we will have turned GBM largely into a chronic disease, like we accomplished for diabetes mellitus and HIV.

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