with the new treatment schedule. This identified a number of biological processes associated with outcome. One of the most prominent biological features associated with survival was overexpression of the epidermal growth factor receptor gene (EGFR). Thus, targeting the EGFR-pathway for which several specific small molecule inhibitors are in clinical evaluation may improve outcome. Most interestingly, a correlated gene set was reminiscent of a "self-renewal" signature defined in a mouse model for leukemia (Krivtsov et al., 2006) that may be indicative of the tumor stem cell population within glioblastoma. The tumor stem cell concept suggests that these cells represent the source of tumor propagation and thus need to be eradicated for successful cure of the patients. This self-renewal signature was associated with worse outcome in patients treated with the combination therapy. This finding may provide first evidence that glioma stem cells are implicated in resistance to chemoradiation therapy in an uniformly treated cohort of glioblastoma patients. Other biological processes associated with outcome are linked to "tumor-host interaction" and comprise tumor stroma, characterized by markers for tumor blood vessels, and innate immune response, that may have important implications for anti-angiogenic therapy and tumor vaccination efforts. Taken together, molecular tumor profiling of uniformly treated patients has provided important insights into mechanisms of chemoradiation resistance that will allow improvement of individualized treatment strategies.

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Targeted intratumoural toxins: background and first clinical results

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Targeted toxins for direct intratumoral delivery into brain tumors rely on two concepts: compartmental selectivity of the targeted molecule and distribution of the agent throughout the tumor due to convective priciples. The whole concept called convection enhanced delivery has been tested in a complex matrix of reagents and clinical settings. Three toxins were generated from a permutated pseudomonas exotoxin (PSET) from which the binding domain was deleted and replaced by a ligand which would bind to a selectively overexpressed receptor on the surface of glioma cells. The substances are IL-4-PSET, IL-13-PSET and TGFα-PSET. Another such molecule is a conjugate of transferrin and diphtheria toxin.
The delivery of these agents is achieved by stereotactically placed intraparanchymal catheters connected to a pump which will deliver volumes up to 12 ul per minute to generate a slow centrifugal flow of the reagents and over days achieve a large area of distribution.
The IL-4-PSET has been used for direct intratumoral infusion and has completed a phase II which still awaits publication. Likewise has TGFα-PSET gone through a phase II, awaits final analysis of the data and further development. The only phase III trials were undertaken with IL-13-PSET (cintredekin besudotox, PRECISE trial) and Transferrin-diptheria toxin (TransMID-tiral).
The PRECISE trial was carried out in the post-resection recurrent glioblastoma setting where up to four catheters were placed intraparenchymally around the resection cavity. Authorities prescribed as comparator for local treatment for recurrent disease Gliadel Wafer. After 215 analysed patients, the overall median survival was 36.4 weeks meaning that the IL-13 compund was indeed more than 25% better than the published prescribed control. However, in a situation where also the control increased to 35.3 weeks (better resections, more experience with the wafers) the study came out inconclusive.
The TransMID trial was based on the intratumoral infusion of the agent via two catheters in non-resectable recurrent tumors in patients with good Karnofsky. This is a very select group of patients resulting in slow accrual. After some more than 50% of the patients were entered and an early interim analysis was prescribed, it appeared to the data monitoring board that the likelihood that the reagent will meet its target was very small so it was recommended to hold the study.
The development of toxin conjugated targets for intratumoral delivery for gliomas is very slow and in addition a very complex process because a very complex and diverse matrix of parameters such as tissue characteristics, catheter design, target selectivity, solubility and many more need to be evaluated and of these only a fraction has been sufficiently analyzed in the current trials. It is likely that convection as a delivery method with the adequate planning tools for catheter placement and modelling of drug distribution can find a place in invasive brain tumor treatment or treatment of other neurological diseases. Whether the reagents tested so far have the required properties of selectivity, efficacy, stability, permeability is still an open question because there are too many uncertainties as to why the trials have been as inconclusive as they have up to the present state.

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Targeted therapies and anti-angiogenic treatments in newly diagnosed malignant glioma

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Better molecular understanding and compelling preclinical rational have led to identification of a number of novel "drugable" targets in malignant glioma. However and despite initial promise, when these drugs were tested in randomized trials in recurrent glioma, they failed to demonstrate consistent anti-tumor activity. Absence of the target in many tumors, inadequate pharmacokinetics or insufficient penetration through the blood-brain barrier, and inability of measuring a cytostatic rather than a cytotoxic effect may be reasons for the apparent lack of activity. Importantly, redundant pathways and escape mechanisms, and primarily resistant (stem) cells contribute to treatment failure. Duration of treatment exposure in the recurrent setting may be too short to demonstrate a clinically meaningful anti-tumor effect.
Testing novel biological compounds in newly diagnosed glioma may be a more successful avenue. The current standard of care of radiotherapy ($\pm$ concomitant temozolomide chemotherapy) adds complexity, as novel agents need to be evaluated with simultaneous administration of cytotoxic chemotherapy and irradiation. This may lead to increased acute and unpredictable late toxicity. However, preclinical rational also suggests synergy of concomitant administration with chemo- and or radiotherapy. Bevacizumab, a monoclonal anti-VEGF antibody has never shown to possess single agent activity against any solid tumor, and cetuximab, a monoclonal anti-EGFR antibody is most effective in combination with chemotherapy or radiation.
The schedule of administration may be of importance, e.g. inhibition of the cell cycle by an EGFR inhibitor may render the tumor cells less susceptible to certain chemotherapy agents. Concomitant administration of an anti-EGFR antibody and radiotherapy will increase the antitumor effect (radiosensitization, as demonstrated for head and neck cancer), while adding an EGFR inhibitor with chemotherapy has failed to prolong survival (in head and neck cancer and non-small cell lung cancer). There is some evidence that anti-angiogenic and anti-vascular agents may selectively normalize tumor vasculature, decreasing edema and intratumoral pressure, consecutively leading to better perfusion of cytotoxic agents and increased anti-tumor effect. Improved tumor oxygenation and cell cycle arrest in G2-M phase make tumor cells more susceptible to irradiation.
A number of uncontrolled pilot phase trials of anti-angiogenic compounds and concomitant chemoradiotherapy in glioblastoma have recently been completed or are ongoing. Cilengitide, a pentapeptide targeting tumor-specifc alphaVbeta3 and alphaVbeta5 integrins has shown some promise in combination with TMZ/RT in newly diagnosed glioblastoma. Ongoing trials are investigating the addition of the protein kinase C (PKC) inhibitor enzastaurin, the VEGFR tyrosine kinase inhibitor (TKI) vatalanib (PTK787) or the combined VEGFR and EGFR TKI vandetinib (ZD6474). However, in order to identify antitumor activity surrogate endpoints including modern imaging, perfusion MRI or amino-acid PET and a randomized phase II design should be considered and correlations with molecular target validation should be sought.

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