Diffusion-Weighted MRI as a Biomarker of Tumor Radiation Treatment Response Heterogeneity

Diffusion imaging has been used to generate investigational biomarkers of treatment effect in glioma. The apparent diffusion coefficient (ADC), like other MR-based imaging biomarkers, is usually measured as a mean over a region of interest, typically the contrast-enhancing portion of the tumor for glioblastoma. Studies have shown that not only are individual glioblastoma heterogeneous tumors, but their response to therapy, including changes in diffusion parameters, can be equally varied. To capture this intratumoral heterogeneity of response, functional diffusion maps (fDM) have been used. fDM are based on changes in diffusion on a voxel by voxel basis, rather than an average change over the entire region of interest (ROI). In a recent publication by Lemasson et al., the authors use an fDM approach to assess radiation treatment effect in a genetically engineered mouse model of glioblastoma. The authors show that radiation treatment induces increased ADC values in tumors. Using an area under the curve (AUC) analysis, mean increase in ADC during treatment correlated with longevity, but the correlation was not strong ($R^2 = 0.46$). However, when an fDM approach was performed assessing only voxels that were significantly increased in ADC (based on a predetermined threshold and referred to as fDM$^+$ voxels), the correlation between the AUC of the fDM$^+$ voxels and survival rose to $R^2 = 0.88$. The authors also showed that apoptosis increased with radiation dose and that the percent of cells staining with the mitotic marker Ki-67 diminished. Thus the relative tumor volume with significantly increasing ADC (i.e., the proportion of tumor with fDM$^+$ voxels) appears to be a superior metric to average change in ADC as a predictor of survival. The results add to a growing body of evidence, both clinical and pre-clinical, that fDM can serve as a way to identify voxels that are most predictive of overall treatment effect and also reflect histopathologic changes. These efforts further support the potential of fDM to generate early response markers that precede tumor size change. Last, fDM may also add value as a way to distinguish regions of tumor that are responding versus those that are not, and thus help identify treatment response which may otherwise go unnoticed.

Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity

Chemotherapy-induced peripheral neuropathy (CIPN) represents the dose-limiting toxicity for several important chemotherapeutics, including taxanes, proteasome inhibitors, vinca alkaloids, and platinum; it also has a substantial impact on quality of life. Oxaliplatin, the 3rd approved platinum drug, is approved for colorectal carcinoma in both the adjuvant setting after potentially curative surgery and for metastatic disease. It is also under study and used off-label for other gastrointestinal malignancies. Its principal dose-limiting toxicity is peripheral neuropathy, which comes in two forms: 1) a unique acute neuropathy, consisting of cold-exacerbated acral and perioral paresthesias sometimes accompanied by pharyngolaryngeal dysethesias, affecting >80% of patients, and 2) a sometimes painful chronic sensory neuropathy in a majority of patients in a cumulative, dose-dependent manner (similar to cisplatin). While the relationship of acute to chronic peripheral neuropathy is unclear, it has been hypothesized that the acute neuropathy is attributable to chelation of calcium by oxalate, a metabolite of oxaliplatin, resulting in development of a Ca-dependent voltage-gated Na channelopathy. This theory led to interest in trying to mitigate oxaliplatin CIPN through the administration of calcium and magnesium salts at the time of oxaliplatin administration. Retrospectively collected data suggested this approach decreased acute and to a lesser extent chronic oxaliplatin neuropathy. Two prospective phase III trials designed to study this question were prematurely closed because an interim analysis of one (ultimately found to be incorrect) suggested that the salts might decrease oxaliplatin’s efficacy. Subsequent analyses from these uncompleted studies showed no evidence that salts decreased acute PN, but one study suggested decreased chronic PN.

Given the importance of this question (currently approximately half of oxaliplatin recipients currently receive prophylactic Ca/Mg),
this North Central Cancer Treatment Group trial enrolled patients having undergone curative intent colorectal surgery scheduled to receive oxaliplatin as part of FOLFOX chemotherapy. Patients with prior neurotoxic chemotherapy, baseline neuropathy, or on agents to prevent or treat neuropathy were excluded. In a double-blind fashion, patients were randomized to Ca and Mg before and after oxaliplatin infusions, placebo before and after, or Ca/Mg before and placebo after. Outcome measures included the recently created and validated patient-determined EORTC sensory neuropathy score (the primary measure) as well as investigator-determined CTCAE grading and an investigator-assigned oxaliplatin-specific scale. The study, which accrued 353 patients, found no benefit of Ca/Mg in preventing several patient-reported measures of acute neuropathy, with only throat discomfort marginally improved with the salts. Nor was there any benefit in preventing chronic sensory neuropathy, either based on a patient-reported scale or time to CTCAE ≥ 2. Thus, this well-powered trial found no evidence that salts are protective. These results, while disappointing, are practice-changing. Although some data suggest that both duloxetine and venlafaxine help alleviate the pain of oxaliplatin neuropathy, the search for a neuroprotective agent must continue.

Reference

CSF-1R inhibition alters macrophage polarization and blocks glioma progression

There has been accumulating interest in the role of tumor associated inflammatory cells in cancer initiation, progression and response to therapy. The subpopulation of interest have been tumor-associated macrophages and in the case of Glioblastoma Multiforme macrophages and microglia (TAMs). TAMs demonstrate a high degree of plasticity in response to the tumor microenvironment and can assume a wide range of roles, capable of both promoting and opposing tumor development. It is recognized that TAMs depend on colony stimulating factor-1 (CSF-1) for differentiation and survival.

In this study Pyontech et al. used a new drug BLZ945, which has high affinity for CSF-1R, a receptor almost exclusively expressed by macrophages and its progenitors in the tumor microenvironment. Using mouse (specific to proneural subtype of GBMs: Nestin NTVa; RCAS hPDGFB; Cdkn2a-/-) and orthotopic (proneural GBM) xenograft models they show that treatment with BLZ945 resulted in increased survival and tumor regression. However, they show that CSF-1R blockade does not result in depletion of TAMs and in fact TAMs continue to survive in response to glioma-secreted factors, including granulocyte-macrophage CSF (GM-CSF) and interferon-g (IFN-g). The authors provide evidence that suggests that the surviving TAMs have been ‘re-educated’ to M1-like macrophages (known to be anti-tumor effectors; Nat. Immunol. 11,889–896 (2010)); and display increased phagocytic properties. In a correlation to their finding they show the proneural (without G-CIMP) GBMs,
which display a gene signature reflective of BLZ945 treated TAMs, have significant survival benefit.

As our knowledge increases in this area with this work some of the questions that arise from these studies are what are the trophic factors secreted by TAMs, that in turn modify glioma cells, what is the mechanism of interaction between BLZ945 and NF-kB signaling pathway, are these results truly specific to proneural subtypes, and why does BLZ945 not result in promotion of TAMs into an M1 phenotype?

Reference