was 39% (95% CI 21–57). No significant correlation was found between clinical outcome measures and the MGMT promoter methylation status or IDH1/2 mutation status.

CD133+ U87 cells exhibit single-agent activity in patients with recurrent GB; upfront combination of axitinib and LOM did not significantly increase progression-free or overall survival in patients with recurrent glioblastoma. Adding CCNU to axitinib after progression seems to result in improved PFS compared to upfront combination therapy.

**P08.10 POSTOPERATIVE HYPOFRACTIONATED ACCELERATED INTENSITY MODULATED RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN THE MANAGEMENT OF PATIENTS WITH NEWLY DIAGNOSED GliOBlastOMA: RESULTS OF A PILOT STUDY**


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**BACKGROUND:** Glioblastoma (GBM) is the most aggressive malignant brain tumor with overall survival ranging from 12–15 months.

**AIMS:** We intended to assess the feasibility and efficacy of combination of hypofractionated accelerated intensity modulated radiotherapy (IMRT) with concurrent and adjuvant temozolomide (TMZ) in postoperative management of patients with newly diagnosed GBM.

**METHODS:** In a single arm phase II study, 25 patients with newly diagnosed, histologically proven GBM with age 18–70 years, Karnofsky performance status ≥ 70 and normal end-organ function were included. Four weeks after maximal safe surgery, patients underwent contrast enhanced planning CT scan. Gross tumor volume (GTV) was defined as enhancing tumor on T1-W post contrast MR or contrast enhanced CT images. Clinical target volume (CTV) included GTV and peritumoral edema with an anatomically constrained expansion of 2 cm. Planning target volume (PTV) encompassed CTV with 0.5 cm isotropic expansion. PTV boost was defined as GTV with 0.3 cm isotropic expansion. IMRT- 60 Gy/25 fractions/3 weeks to PTV boost, 50 Gy/25 fractions/5 weeks to PTV was delivered by simultaneous integrated boost technique with 4–9 coplanar beams. TMZ was administered in concurrent and adjuvant setting as per EORTC/NCIC regimen. Primary study endpoint was progression free survival (PFS) and secondary endpoints were overall survival (OS) and late toxicity assessment. Survival analysis was done by Kaplan-Meier method.

**RESULTS:** The median age was 50 years (male: female ratio of 18:7). Median KPS was 80. The most common tumor site was frontal (44%) followed by temporal lobe (25%). The extent of surgery was gross total, near total and sub-total in 44%, 24% and 32% of patients respectively. Median D95 PTV was 98.57% of prescribed dose. Median VPTV95% was 99.46%. Median conformity and homogeneity (D2/D98) indices were respectively 1.05 and 1.1. Twenty three (92%) patients completed the planned RT course. Median number of cycles of adjuvant TMZ administered was 5. Severe (grade 3/4) toxicities included acute CNS effects in 2 (during RT), leucopenia in 1, neutropenia in 3 and thrombocytopenia in 2 patients (during adjuvant TMZ). After a median follow-up of 19.07 months, disease progression or death was observed in 80% of patients. Six patients developed isolated brain recurrence. Median PFS and OS were 14.2 months and 21.3 months respectively. The actuarial median progression free survival (PFS) and overall survival (OS) were 14.2 months and 21.3 months respectively. The actuarial median progression free survival (PFS) and overall survival (OS) were 14.2 months and 21.3 months respectively. The actuarial median progression free survival (PFS) and overall survival (OS) were 14.2 months and 21.3 months respectively. The actuarial median progression free survival (PFS) and overall survival (OS) were 14.2 months and 21.3 months respectively.

**CONCLUSIONS:** Our interim data suggest that this study design is feasible. PFS and OS were inferior compared to what is expected from the modern phase III trials. Given the promising outcomes of the Phase III trials of Tumour Treating Fields (TTFields) in both primary and recurrent adult Glioblastoma Multiforme (GBM), a fourth treatment modality has emerged. TTFields therapy utilises low intensity (1.5–3 V/cm), intermediate frequency (200 kHz) alternating electric fields delivered through external electrodes attached to the patient’s scalp. The modest improvement in median overall survival has provided legitimacy to the physical modality, but also scepticism among academics and clinicians alike. Overall, TTFields have been shown to be safe when used as a monotherapy and in combination with TMZ. We have commenced TTFields in a prospective Phase II trial for postoperative management of patients when used as a monotherapy and in combination with Temozolomide but the underlining mechanisms behind this still have yet to be elucidated. TTFields efficacy is limited by patient compliance with the external battery pack and electrode system and voltage intensity is limited by delivery through the skin, subcutaneous tissues, and bone. This may influence the outcome of delivering a therapeutic electromagnetic field to high grade brain tumours via a completely internalised system.

**Medtronic Deep Brain Stimulation (DBS) electrodes were inserted into standard cell culture flasks and used to deliver electric fields over a variety of different voltages and frequencies to a panel of adult, paediatric and primary GBM cell lines. Cell viability was assessed with Presto Blue assay and gene expression was analysed with quantitative RT-PCR. Cell cycle analysis was performed through FACS. The synergistic effects of chemotherapeutic agents known to act on the mitotic apparatus were also assessed.**

**DBS electric fields reduce cell viability of a range of different cell lines in a dose- and frequency-dependent manner. Cell viability was reduced by up to 55% and 61% in dose-dependent manner over the range of voltages for a 7 day treatment - 0V to 10V for U87 cells (Two-way ANOVA, p<0.0014) and SF188 cells respectively (n=2). Cell counts were taken of treated U87 and SF188 cell line and a reduction of 86% and 62%, with greatest in proportion of cells within the region of close proximity to the electrode. We examine synergistic effects with mitotic inhibitor agents.**

**Electric fields delivered through DBS electrodes exhibit anti-proliferative effect on GBM cell lines, with a clear dose-response curve in terms of applied voltage. This is evident at frequencies substantially lower than those used in NovoTTF therapy and may represent a different biological effect e.g. interference with ion channel function. Overall, implanted DBS electrodes may provide a novel therapeutic avenue for the treatment of brain tumours.**