

## CHEMOTHERAPY IN HIGH-GRADE GLIOMA

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High-grade glioma are the most common primary brain tumours and occur at a rate of 5 cases per 100.000 per year. They are most devastating cancers, causing progressive disability with a spiralling-down evolution leading to death in most cases. They represent a major cause of death in young and active patients, therefore even moderate improvement in survival could result in an appreciable number of years of life saved. They are by nature infiltrative and a complete surgical resection almost never occurs and many patients suffer from severe neurological deficits. A number of prognostic factors have been identified and include age, grade, KPS, amount of surgical resection, mental status and can be grouped in recursive partitioning analysis (RPA) classes. For example, differences in survival according to RTOG RPA I to VI classes reveal much larger differences than any known therapeutic intervention, making any treatment evaluation outside randomized trials fairly hazardous. For the time being, post-operative radiotherapy (PORT) remains the most efficient and widely used form of non-surgical treatment. Six randomized trials compared post-operative RT to surgery alone, or surgery with chemotherapy, and in five the risk ratio favoured PORT, with an overall rate of 0.81 ( $p < .00001$ ). Numerous forms of RT, including non-conventional RT doses and fractionations, particle therapy, brachytherapy and intra-operative RT, have been tested with controversial results. In spite of its efficacy, PORT alone is associated with modest survivorships, with MST ranging between 9 and 12 months.

Post-operative chemotherapy, using mainly nitrosoureas has been tested for the past 30 years. The choice of these compounds was mainly due to the fact that they are lipid-soluble and cross the blood-brain barrier. So far, 3 meta-analyses have been done, the last one including 12 available trials. Overall, hazard ratio was in favour of chemotherapy (0.85,  $p < .0001$ ) but the gain in 1 and 2-yr survival was only 6% and 5%, respectively. Apart from the nitrosoureas, other agents have been tested or are currently being tested, including Procarbazine, Oxaliplatin, Carboplatin, Vincristine, Irinotecan, CPT-II and Taxol. However, the most widely studied drug in the past few years has been Temozolomide, a novel alkylating agent. TMZ is rapidly absorbed after oral administration and readily crosses the blood-brain barrier. It was shown to have a good activity in recurrent high-grade glioma. The rationale for combining TMZ and RT is based on preclinical data suggesting at least additive activity. TMZ induces a G2-M arrest in glioma cells, a most radiosensitive phase of the cell cycle. In a phase II study where 64 patients received RT to 60 Gy with concomitant TMZ (75 mg/m<sup>2</sup> qd), followed by adjuvant TMZ (200 mg/m<sup>2</sup> qd x 5 days every 4 wks x 6 cycles), a median survival of 14.3 months (10.4 - 18.3) was observed, with a MST of 17 months for patients under 50 years of age. These promising results led to EORTC 26981/22981, where 573 patients were randomized between RT alone (60 Gy at 2 Gy per fr) and RT combined with TMZ using the same scheme as in the previous phase II trial. Results of this study are not yet available. In the meantime, the EORTC Radiotherapy and Brain Tumour Groups are devising new approaches, where novel agents will be incorporated into studies with RT with or without TMZ. These agents will include anti-angiogenic agents, Cox-2 inhibitors, EGFR inhibitors and Farnesyl-transferase inhibitors. On the basis of preclinical studies, these four categories of "targeted" therapies interact on the molecular level with ionising radiation. It is hoped that the addition of these novel compounds will enhance the effect of radiotherapy and chemotherapy in high-grade glioma.