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Topic: Brain tumor cell invasion and metastasis: anatomical, biological and clinical considerations

Gemcitabine followed by radiotherapy in treatment of newly diagnosed high-grade gliomas

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ABSTRACT

Aim: High-grade glioblastoma multiforme (GBM) has a poor median overall survival (OS). The standard treatment after surgery is temozolomide and radiotherapy (RTH). Patients with unmethylated methylguanine-methyltransferase promoter (MGMT) have no or little benefit from temozolomide and are eligible for alternative therapies. Gemcitabine is a good radiosensitizer. We aimed to evaluate the combination of gemcitabine with RTH in newly diagnosed GBM. **Methods:** The study was a prospective phase II study. Eligible patients were required to have histologically proven anaplastic astrocytoma or GBM. Patients underwent biopsies or subtotal resection. The treatment consisted of fixed-dose rate gemcitabine 175 mg/m^2 weekly followed after 24 h by standard cranial RTH for 6 weeks. Tumor response was evaluated by Macdonald criteria. In case of progression, patients received temozolomide (200 mg/m^2/5 days every 28 days). **Results:** Thirty patients with a median age of 52 years (30-69), 73%/27% male/female, the Eastern Cooperative Oncology Group performance status 1 (range 0-2) were enrolled. Five patients had a partial-response (17%) and 13 stable-disease (43%). Median time to progression was 7.88 months (95% CI 6.1-9.69) and OS was 11.77 months (95% CI 9.97-13.56). The treatment was well tolerated with grade-3 neutropenia in 3, grade-3 anemia in 2 and impaired liver enzymes in 1 patient. **Conclusion:** Gemcitabine followed by radiotherapy is active and promising regimen in newly diagnosed GBM. Gemcitabine uptake is easy, with a long local retention of active metabolites, precluding systemic side effects of radiosensitization. In a phase III study this treatment should be evaluated in patients with unmethylated MGMT promoter who will not benefit from temozolomide.

Key words: Gemcitabine; radiation; glioblastoma multiforma; temozolomide

INTRODUCTION

Malignant gliomas grade 3 anaplastic astrocytoma (AA) or grade 4 glioblastoma multiforme (GBM) are rapidly progressing primary brain tumors, which in spite of advances in surgery, radiotherapy and chemotherapy, remain associated with high morbidity and mortality.[1] Despite the current multimodality therapy, the overall median survival for newly diagnosed patients is 10 months for patients with GBM and 2-3 years for those with AA.[2,3]

Standard treatment of malignant gliomas is surgery, followed by radiotherapy concomitant with temozolomide (TMZ), followed by adjuvant TMZ (Stupp *et al*.,[2] 2005). Surgery followed by involved field radiotherapy up to total dose of 60 Gray (Gy) significantly prolongs survival. There have been many efforts to intensify radiotherapy, including the use of radiosenstizers, brachytherapy, radioactive seeds implanted in the tumor bed, and stereotactic radiosurgery in selected cases.[4]

Initially the routine use of chemotherapy in addition to cranial irradiation was controversial. Individual randomized, controlled studies demonstrated no significant improvement in median survival with single agent or multiple agents chemotherapy, although a significant increase in survival was noted in a meta-analysis.[1] There was a significant

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