Role of gemcitabine as a radiosensitizer in Glioblastoma Multiforme treatment

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Abstract

Treatment for glioblastoma multiforme comprises of surgical resection of the tumour followed by radiotherapy and chemotherapy. Temozolomide is the routinely used radiosensitizer during radiotherapy and chemotherapy cycles and has shown good results. An alternative to temozolomide is gemcitabine, which is still under evaluation for use as a potential radiosensitizer. We review the current evidence for the efficacy and safety of gemcitabine as an alternative to temozolomide in GBM treatment including those cases of GBM that do not respond to standard post-operative temozolomide therapy.

Keywords: Glioblastoma multiforme (GBM), Radiosensitizer, Gemcitabine.

Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumour in adults with a poor prognosis. Treatment options include cytoreductive surgery followed by radiotherapy (RT), and systemic chemotherapy as adjuvant treatment.[1] Gemcitabine is a radiosensitizer that is routinely used for treatment of solid tumours such as small cell lung carcinoma, breast and ovarian cancer, bladder cancer and pancreatic cancer. It is now being considered for use in GBM therapy.[2,3] The positive interaction between gemcitabine and radiotherapy is likely due to a combination of mechanisms that include deoxyadenosine triphosphate depletion, cell cycle redistribution and inhibition of DNA synthases and repair.[2] Gemcitabine can be deaminated to its metabolite difluorodeoxyuridine (dFdU), also a radiosensitizer.[3]

Review of Evidence

Sigmond et al. conducted a Phase 0 study to demonstrate that gemcitabine passes through the blood brain barrier (BBB). This study also evaluated whether gemcitabine converted to its active form inside tumour cells. Ten patients with recurrent GBM were administered intravenous gemcitabine 1-4 hours before surgery, and the samples taken through biopsy were evaluated for presence of gemcitabine. The tumour cells not only showed the presence of gemcitabine and its metabolites, there was no difference in drug levels between plasma and tissue, confirming that gemcitabine readily passes BBB in GBM patients. Gemcitabine and dFdU concentrations in the tumour cells were also found to be high enough to allow radiosensitization.[4]

A Phase II multicenter study was conducted to evaluate effect of gemcitabine on patients with grade III or IV astrocytoma and GBM at first relapse. These patients were already on steroids and had received chemotherapy and RT. The median duration of stable disease was only 2.7 months (range 0.9-11.2) and no objective response was observed.[5] The study hinted at the possibility that dexamethasone may inhibit cytotoxicity of gemcitabine as seen in in-vitro glioma models.[6]

Another Phase II study was done to evaluate the efficacy of pre-irradiation gemcitabine therapy. Twenty-one newly diagnosed GBM patients who had not received prior RT or chemotherapy were enrolled and were given up to four monthly cycles of intravenous gemcitabine. RT was given afterwards but in the case of disease progression or gemcitabine intolerance it was given earlier. This trial demonstrated that gemcitabine followed by RT is safe to use in newly diagnosed patients with GBM. However this study did not demonstrate that the gemcitabine schedule followed here gave added survival advantage over standard field RT alone.[7]

A non-randomized Phase II study was done by the same authors to see the effect of pre-radiation combination therapy of gemcitabine and treosulfan (GeT). Seventeen newly diagnosed GBM patients were enrolled in this study and were given up to four cycles of intravenous GeT followed by RT. Radiotherapy was given earlier if there was disease progression. The median overall survival was 12 months and GeT combination produced significant haematological toxicity. The schedule used in this study for administering GeT did not demonstrate significant survival advantage over standard RT alone. The results of this study again were not convincing.[8]

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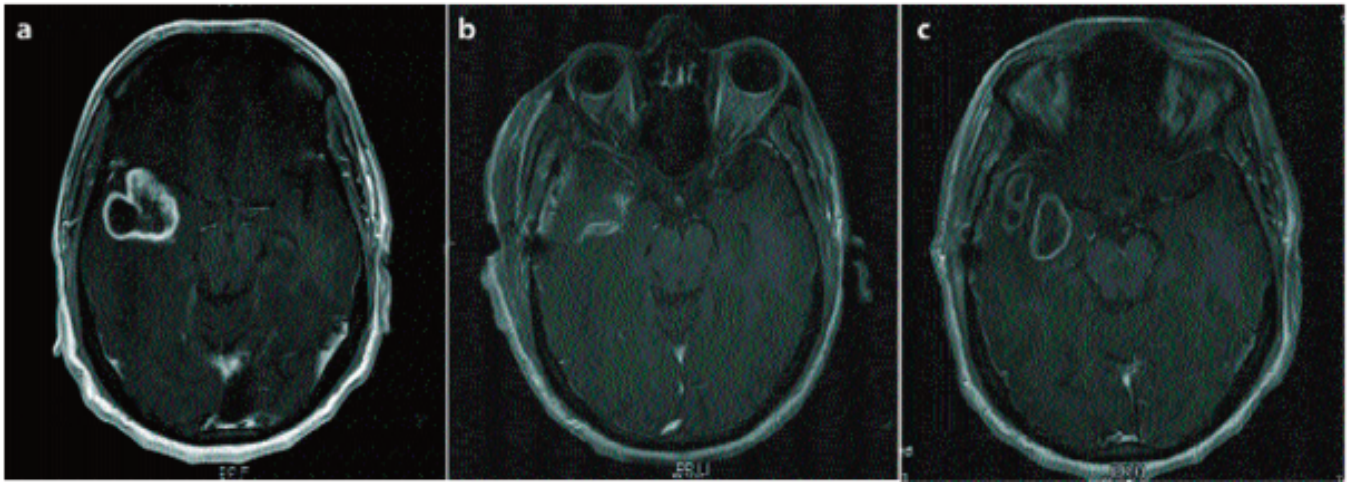

Figure-1: a) MRI Axial T1WI with contrast showing right temporal GBM. b) Post-operative MRI Axial T1WI with contrast, showing gross total resection. c) 6-months follow up MRI Axial T1WI with contrast showing recurrent disease.

Fabi et al., conducted a Phase I study to evaluate the association of gemcitabine and RT as first line therapy for GBM instead of temozolamide and RT, and to determine the dose-limiting toxicity and maximum tolerated dose (MTD) of gemcitabine. Patients were given gemcitabine before RT and then with RT. Based on the results they recommended a fixed dose-rate gemcitabine at 175 mg/m^2/weekly for further evaluation in a Phase II study that was in progress at that time.[9]

Metro and Fabi et al., in their Phase II study also investigated the activity of chemo-radiotherapy in O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.[8] Gemcitabine and RT were given concomitantly. At 175 mg/m^3/week gemcitabine produced a response rate of 17.5% with a median duration of 18 months and a remarkable disease control rate of 78%. This time no neurological deterioration was observed as seen in the Phase I study, or haematological toxicity. A disease rate of 77.5% was observed in patients with unmethylated MGMT promoter and 91% in methylated MGMT promoter, suggesting gemcitabine as a better radiosensitizer in patients who get little or no benefit from the use of temozolomide.[10]

Kim et al. evaluated the toxicity and preliminary efficacy of increasing doses of gemcitabine in newly diagnosed high grade glioma. Gemcitabine was started in the last 2 weeks of RT, when the BBB is readily breached, starting at a dose of 500 mg/m^3/week. The MTD of gemcitabine was 750 mg/m^3/week with acute reversible haematological toxicity being the most common side effect. Median overall survival was 26.5%. Hence, this study demonstrated favourable outcome of gemcitabine when used concurrently with RT.[11]

Conclusion

Gemcitabine and its metabolite, dFdU both are radiosensitizers that easily cross the BBB and reach high concentrations within tumour cells. When given alone or in combination with treosulfan before RT, gemcitabine does not appear to yield promising results. Concomitant RT and gemcitabine have shown good results in newly diagnosed GBM cases. Gemcitabine may be a better radiosensitizer in patients who do not respond well to temozolamide. When given concurrently with RT for HGG, gemcitabine has shown favorable results. Overall, gemcitabine is a safe radiosensitizer that may be used for treatment of GBM together with RT in patients not tolerating or not responding to temozolamide, however it needs more studies to establish its role as an alternative to temozolamide.

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