Clinical Neurology and Neurosurgery 115 (2013) 1814–1819

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Factors predicting temozolomide induced clinically significant acute hematologic toxicity in patients with high-grade gliomas: A clinical audit☆

Tejpal Gupta[a,*], Sarthak Mohanty[a], Aliasgar Moiyadi[b], Rakesh Jalali[a]

[a] Department of Radiation Oncology, Advanced Centre for Treatment Research & Education in Cancer (ACTREC) and Tata Memorial Hospital (TMH) Tata Memorial Centre, Mumbai, India
[b] Neuro-surgical Unit, Department of Surgical Oncology, Advanced Centre for Treatment Research & Education in Cancer (ACTREC) and Tata Memorial Hospital (TMH), Tata Memorial Centre, Mumbai, India

ARTICLE INFO

Article history:
Received 10 April 2013
Received in revised form 30 April 2013
Accepted 15 May 2013
Available online 12 June 2013

Keywords:
Glioma
Myelo-toxicity
Neutropenia
Temozolomide
Thrombocytopenia

ABSTRACT

Introduction: Myelo-suppression, the dose-limiting toxicity of alkylating cytotoxic agents is generally perceived to be uncommon with temozolomide (TMZ), a novel oral second generation imidazotetrazinone prodrug, with a reported incidence of 5–10% of grade 3–4 acute hematologic toxicity. We were observing a higher incidence of clinically significant myelo-toxicity with the standard schedule of TMZ, particularly in females, prompting us to do a clinical audit in our patient population.
Methods: One hundred two adults (>18 years of age) treated with TMZ either for newly diagnosed or recurrent/progressive high-grade glioma constituted the study cohort. Clinically significant acute hematologic toxicity was defined as any one or more of the following: any grade 3–4 hematologic toxicity; omission of daily TMZ dose for ≥3 consecutive days during concurrent phase; deferral of subsequently due TMZ cycle by ≥7 days during adjuvant phase; dose reduction or permanent discontinuation of TMZ; use of growth factors, platelets or packed-cell transfusions during the course of TMZ. Uni-variate and multi-variate analysis was performed to correlate incidence of acute hematologic toxicity with baseline patient, disease, and treatment characteristics.
Results: The incidence of clinically significant neutropenia and thrombocytopenia was 7% and 12% respectively. Seven (7%) patients needed packed-cells, growth factors, and/or platelet transfusions. Grade 3–4 lymphopenia though common (32%) was self-limiting and largely asymptomatic. Two (2%) patients, both women succumbed to community acquired pneumonia during adjuvant TMZ. Multi-variate logistic regression analysis identified female gender, grade IV histology, baseline total leukocyte count <7700/mm^3 and baseline serum creatinine ≥1 mg/dl as factors associated with significantly increased risk of clinically significant acute hematologic toxicity.
Conclusion: The incidence of TMZ induced clinically significant neutropenia and thrombocytopenia was low in our patient population. Severe lymphopenia though high was largely asymptomatic and self-limiting. Gender, grade, leukocyte count, and serum creatinine were significant independent predictors of severe acute myelo-toxicity.

1. Introduction

The contemporary standard of care for newly diagnosed supratentorial glioblastoma, the most common malignant primary brain tumor in adults, consists of maximal safe resection followed by conventionally fractionated focal conformal radiotherapy with concurrent and adjuvant temozolomide (TMZ) chemotherapy [1,2]. The improved efficacy and perceived low toxicity of this regimen has prompted its widespread adoption by the neuro-oncology community worldwide [3,4]. TMZ has also shown significant benefit as salvage therapy in previously treated recurrent, progressive high-grade gliomas [5] and is now also being increasingly offered to patients with anaplastic astrocytoma, oligodendroglioma, and mixed oligoastrocytoma in the post-operative adjuvant setting [6,7]. It is a novel oral second generation imidazotetrazinone prodrug [8] that undergoes spontaneous conversion under physiological conditions to its active alkylating moiety

☆ Presented in part at Joint 10th Annual Meeting of the Asian Society for Neuro-Oncology and 5th Annual Meeting of Indian Society of Neuro-Oncology (ASNO 2013) held from 21st to 24th March 2013 at Mumbai, India.

* Corresponding author at: Radiation Oncology, ACTREC & TMH, Tata Memorial Centre, Kharghar, Navi Mumbai 410210, India. Tel.: +91 22 27405057; fax: +91 22 27405061.
E-mail address: tejpalgupta@rediffmail.com (T. Gupta).

0303-8467/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.clineuro.2013.05.015

5-(3-methyl)1-triazen-1-yl-imidazole-4-carboxamide (MTIC). MTIC is further hydrolyzed to methylhydiazonium which transfers methyl group to DNA, and 5-aminoimidazole-4-carboxamide, the final inactive degradation product which is excreted via kidney [9]. The main mechanism of TMZ-mediated cytotoxicity is methylation of DNA. This cytotoxic action is caused by methylation of the O^6-position of guanine leading to the generation of O^6-methylguanine DNA adducts with additional alkylation at the N^7-position [8,9]. Methylguanine methyltransferase (MGMT) when present, removes DNA adducts and reduces clinical activity. TMZ does not require any enzymatic demethylation in the liver for activation and its metabolism has not been shown to be affected by mild to moderate renal or hepatic dysfunction.

Myelo-suppression, the dose-limiting toxicity of most alkylating cytotoxic agents is generally perceived to be rather uncommon with TMZ with a reported incidence of 5–10% of grade 3–4 myelotoxicity [1,10]. The perceived favorable safety profile of TMZ has prompted its usage even in low-grade gliomas [11] as well as for protracted duration [12] and dose-intense schedules [13,14] in high-grade gliomas. Severe hematologic adverse events are now increasingly being reported even with standard schedules of TMZ necessitating aggressive supportive care with platelet transfusions and growth factors support with attendant resource implications.

In our neuro-oncologic practice [15] we have been using the standard schedule of oral TMZ concurrently (75 mg/m^2 daily) throughout the course of conventionally fractionated focal conformal radiotherapy (59.4–60 Gy in 30–33 fractions over 6–6.5 weeks) followed by adjuvant TMZ (150–200 mg/m^2 days 1–5, every 4-weekly) for 6–12 cycles in patients with newly diagnosed glioblastoma. For patients with progressive/recurrent disease, our salvage regimen is similar to the adjuvant setting. The 1st cycle of adjuvant/salvage TMZ is typically prescribed as 150 mg/m^2 which is subsequently increased to 200 mg/m^2 for subsequent cycles in absence of any demonstrable hematologic toxicity. In case the absolute neutrophil count (ANC) falls below 1500/mm^3 and/or platelet count below 1,00,000/mm^3, TMZ is temporarily withheld till sufficient myelo-recovery. Growth factor support is instituted only when ANC is <500/mm^3 and platelet transfusions are recommended only for platelet count <20,000/mm^3. We do not apply any dose reductions of TMZ during the concurrent phase, however, during the adjuvant phase or in the salvage setting, TMZ dose reductions are recommended as per standard guidelines. Most of these patients also continue to receive other concomitant medication such as anti-convulsants, anti-emetics, H2-blockers, and trimethoprim-sulphamethoxazole that can further potentiate myelo-suppression. We recommend pneumocystis jiroveci pneumonia prophylaxis throughout the course of concurrent chemo-radiotherapy. Such prophylaxis is not used routinely during the adjuvant phase (standard 5-day schedule), but only when absolute lymphocyte count is <500/mm^3. We do not prescribe steroids (dexamethasone) routinely during adjuvant therapy but only on clinical/neurologic worsening or radiological evidence of significant post-treatment changes. We were observing a higher incidence of clinically significant myelo-toxicity, particularly in females, than was previously reported and with growing literature substantiating the premise, were prompted to do a clinical audit of TMZ-related acute myelo-toxicity in our patient population.

2. Materials and methods

Patients of malignant gliomas treated on several Institutional Review Board (IRB) approved study protocols at our research campus over a 3-year period were identified from an electronic database. All patients had provided informed consent for the specific study protocol on which they were treated. Adult patients (>18 years of age) treated with at least a single dose of TMZ either for newly diagnosed or recurrent/progressive high-grade glioma (glioblastoma and variants, anaplastic oligodendroglioma, anaplastic astrocytoma, and mixed anaplastic oligoastrocytoma) were included in this study. Patients receiving an investigational new drug in addition to TMZ were excluded. Their case files and electronic medical records were reviewed thoroughly to extract demographic profile (age, gender); relevant clinical characteristics (histology, grade, weight, height, body surface area (BSA), body mass index (BMI), steroid usage; anti-convulsant usage; and complete blood counts (CBC) at baseline before starting of concurrent TMZ, subsequently at least once weekly throughout radiotherapy, and just prior to every cycle of 4-weekly adjuvant/salvage chemotherapy. Acute myelo-toxicity was assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3) [16]. It is common practice to withhold/defer TMZ or apply dose reductions for grade 1–2 neutropenia or thrombocytopenia. To capture this, we used a stringent though somewhat arbitrary definition of clinically significant acute hematologic toxicity. Clinically significant acute hematologic toxicity was defined as any one or more of the following: any CTCAE grade 3–4 hematologic toxicity; omission of daily TMZ dose for $\geq$3 consecutive days during concurrent phase due to fall in blood counts; deferral of subsequently due adjuvant TMZ cycle by $\geq$7 days due to incomplete myelo-recovery; dose reduction or permanent discontinuation of TMZ; and use of growth factors, platelets or packed-cell transfusions during the course of TMZ. Any delay, dose reduction, or permanent discontinuation of TMZ due to non-hematologic reasons (nausea/vomiting, financial/social considerations, or disease progression) was not considered in this definition. Apart from any severe acute hematologic toxicity, separate analyses were also done for the two most relevant and important cytopenias, i.e. neutropenia and thrombocytopenia using similar criteria. Uni-variate analysis was performed to correlate incidence of clinically significant hematologic toxicity with baseline patient, disease, and treatment characteristics that were categorical and dichotomized at their median value wherever appropriate. Those covariates that had potential association with risk of developing severe hematologic toxicity ($p < 0.2$ on Pearson's chi-square analysis) were considered for multi-variate binary logistic regression analysis. Results of the multi-variate analyses were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). All analyses was done using SPSS version 20.0

3. Results

We identified a total of 107 adult patients with malignant gliomas that had received at least one course of TMZ chemotherapy on various IRB-approved protocols during the period 2010–2012. One child and 1 adult with missing data and 3 adults treated with an investigational new drug in addition to TMZ were excluded thereby leaving 102 patients that constituted our study cohort. The baseline characteristics of the study cohort are described in Table 1.

The overall incidence of any clinically significant acute hematologic toxicity was 40% (41 of 102 patients). Severe lymphopenia (32%) was by far the most commonly encountered clinically significant acute hematologic toxicity, although it was largely asymptomatic and self-limiting. The incidence of clinically significant anemia, leucopenia, neutropenia, and thrombocytopenia was 2%, 7%, 7% and 12% respectively, with a 13.5% (14 of 102 patients) incidence of severe combined neutropenia and/or thrombocytopenia. Seven (7%) patients needed either packed-cell transfusion (1%), and/or growth factor support (5%), and/or platelet transfusions (5%), mostly during the concurrent phase of treatment.