Title

Clinical correlates of severe thrombocytopenia from temozolomide in glioblastoma patients

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Abstract:

Introduction: This study was done retrospectively to evaluate rates of thrombocytopenia and their clinical impact during chemo-radiotherapy for glioblastomas and to elucidate associated clinical factors.

Methods: Sixty-four patients who received temozolomide chemotherapy at our institution were included. Thirty-five patients received full dose chemo-radiotherapy as per the STUPP protocol (Group A) and nine patients received abbreviated radiotherapy with concurrent chemotherapy (Group B). Twenty patients received temozolomide alone with an intended twelve cycles of therapy for first relapse at least six months after completion of adjuvant chemotherapy (Group C).

Results: In group A, twenty-seven of thirty-five (77%) patients completed chemo-radiotherapy phase. 14% had grade 3-4 thrombocytopenia leading to discontinuation. Sixteen of twenty-seven (59%) patients completed adjuvant chemotherapy. There were no grade 3-4 thrombocytopenias but 4% discontinued due to grade 2 thrombocytopenias. In Group B, four out of nine (45%) patients completed chemo-radiotherapy phase. 11% had grade 3-4 thrombocytopenias and discontinued treatment. Three out of four (75%) patients completed adjuvant chemotherapy. Of these, 75% had grade 3-4 thrombocytopenias but none discontinued. Lastly, in Group C, eight out of twenty (40%) patients completed with 10% discontinuing due to thrombocytopenias and the rest due to disease progression. In exploratory analyses, being female increased the risk of myelosuppression and there was a trend noticed in patients

having a higher body surface area.

Conclusion: Our toxicity data was within range of the literature. We identified the group of patients that have increased thrombocytopenia risk. Larger pooled retrospective series and prospective studies are required.

Introduction

High-grade gliomas or glioblastomas are the most common form of primary brain cancers in adults and confers a poor prognosis. In Australia, glioblastomas account for 1.4% of all cancer cases and 3% of cancer deaths (1). Standard treatment for newly diagnosed patients includes maximal surgical resection followed by chemo-radiotherapy for six weeks and then six cycles of adjuvant monthly temozolomide chemotherapy (2). The survival data demonstrated was modest with an increased median survival of 14.6 versus 12.1 months compared to radiotherapy alone (HR 0.63 $P < 0.001$). Stupp *et al* described post-operative treatment as reasonably well tolerated since 85% of participants completed the full course of chemo-radiation as planned (2). However, only 47% of patients completed the planned six cycles of adjuvant temozolomide, representing 37% of those who started treatment. The main reason for this was attributed to disease progression and only 8% discontinued due to toxicity. The main toxicity reported was grade 3-4 thrombocytopenia, with 3% of patients experiencing this in the chemo-radiation period and 11% of patients in the adjuvant chemotherapy period.

Subsequently, there has been a single center report by Gerber *et al* suggesting that toxicity could be severe in a significant minority of patients, mainly due to myelosuppression (3). They found that a lower proportion (only 23%) completed the whole protocol. Toxicity was also higher with 23% of patients discontinuing due to myelosuppression, three-fold that seen in the Stupp *et al* publication. Overall, 19% of patients experienced grade 3-4 thrombocytopenia (80% of these occurring during the chemo-radiation phase and 20% during the adjuvant

phase) with a median duration of thirty-two days. However, two patients (4%) suffered prolonged thrombocytopenia and one died of this complication. There were no significant correlations between clinical factors and myelosuppression identified by Gerber *et al.*

We initiated this analysis because of our concern of the risk of life threatening haemorrhage from thrombocytopenia in this group of patients with an increased risk of falls from impaired mobility and seizures as complications from their disease.

Herein, we report on our own institutional experience with the toxicity of post-operative temozolomide. In addition to adding further data regarding this problem, we also examined for possible contributory factors and the impact of the subsequent dose delays and dose reductions on patient outcomes.

Methods

The study was approved by the Austin Health Human Resources Ethics Committee (HREC). All patients who were prescribed oral temozolomide treatment for glioblastomas were identified through our pharmacy records from 1st July 2011 to 31st December 2013. Data was extracted by the primary author (SA) using a standardized template. Data extracted included patient demographics, tumour characteristics, treatment received, baseline haematological and biochemical parameters and toxicity. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Thrombocytopenia grading is as follows: Grade 1 <LLN –

75,000/mm³, Grade 2 <75,000 – 50,000/mm³, Grade 3 <50,000 – 25,000/mm³ and Grade 4 <25,000/mm³.

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Patients were subsequently divided into three groups (Figure 1). Group A received standard chemo-radiation with radiotherapy given as 60 Gray in 30 fractions with concurrent daily temozolomide (75mg/m²) as per the STUPP protocol. Adjuvant temozolomide was dosed at 150-200mg/m² on days one to five of each twenty-eight day cycle and a planned total of six cycles were given. Group B received an abbreviated course of radiotherapy given as 40 Gray in 20 fractions with concurrent temozolomide (75mg/m²) and adjuvant temozolomide (150-200mg/m²) for six months if feasible. This group was selected based on the treating physician discretion that the patient would not tolerate full dose treatment and largely consisted of a combination of higher comorbidities, age, disease related symptoms and worse performance status. Lastly, we also examined a group (Group C) that received temozolomide alone with an intended twelve cycles of therapy for first relapse at least six months after completion of adjuvant chemotherapy as per the STUPP protocol. The purpose of this was to compare the toxicity of temozolomide immediately following chemo-radiation (Group A) versus temozolomide alone (Group C).

Summary statistics for demographic and treatment variables were generated. Differences in categorical baseline characteristics between patients in Groups A, B and C who completed or discontinued temozolomide, both during radiotherapy and during the adjuvant component, were analyzed using chi square testing.

Results

Patient Demographics

A total of sixty-four patients newly diagnosed or previously diagnosed with glioblastoma were prescribed temozolomide through our institution's pharmacy from 1st July 2011 to 31st December 2013. The median age was fifty-seven years, 55% of the patients were male, 81% patients had grade 4 gliomas and 63% had macroscopic debulking. The demographics of these patients are shown in Table 1. Forty-four of these patients received chemo-radiotherapy. Of this group, thirty-five patients received full dose chemo-radiation (Group A) and nine patients received abbreviated radiotherapy (Group B). Comparing these two groups, the main difference between Group A and B was that Group B was significantly older, with median age of sixty-four years in Group A versus seventy-three years in Group B ($p=0.014$), and was also more likely to have received a biopsy only (67% versus 17%, $p=0.011$). There were twenty patients in a third group (Group C) who received temozolomide only at first recurrence. All of these patients had previously completed full-dose chemo-radiotherapy and adjuvant chemotherapy. In this group, the median age was fifty-two years, 35% of patients were male, 55% had grade 4 gliomas and 55% had macroscopic debulking compared to 45% who had biopsies only. This group was included in our analysis as a comparator group to determine toxicities with temozolomide in the absence of proximity to radiotherapy. All of our patients had received the institutional standard of prophylactic trimethoprim and sulfamethoxazole as *Pneumocystis jiroveci* pneumonia prophylaxis.

Treatment completion rates and clinical course

Group A

In Group A, twenty-seven of thirty-five (77%) patients completed chemo-radiation phase and then proceeded to adjuvant chemotherapy alone. Of the eight patients in Group A who did not receive adjuvant chemotherapy, the reasons include five patients with thrombocytopenias, one patient who had an intra-cerebral haemorrhage with normal platelet counts, one patient with disease progression and one patient who declined adjuvant chemotherapy. Overall, during the chemo-radiation phase of treatment, there were 14% of patients with grade 3-4 thrombocytopenia (Table 2).

For the twenty-seven patients who proceeded to adjuvant treatment in Group A, only sixteen patients (59%) completed their intended course while seven patients discontinued due to disease progression, two patients with clinical deterioration, one patient with grade 2 thrombocytopenia and one patient with a sudden cardiac arrest. There were no observed grade 3-4 thrombocytopenias in the adjuvant phase of Group A. Overall, only sixteen of thirty-five (46%) completed the full course and 17% ceasing for thrombocytopenia.

Group B

In Group B, four of nine (45%) patients completed chemo-radiation phase and then proceeded to adjuvant chemotherapy alone. Of these five patients in Group B who did not proceed to adjuvant chemotherapy, the reasons included three with clinical deterioration, one patient with thrombocytopenia and one patient had an intracerebral haemorrhage in the absence of thrombocytopenia. During

the chemo-radiation phase, 11% patients had grade 4 thrombocytopenia (Table 3).

Of the four patients in Group B who started adjuvant chemotherapy, three patients completed their adjuvant chemotherapy course while one patient did not due to clinical deterioration. There was an observed 75% grade 3-4 thrombocytopenia in the adjuvant phase of Group B (Table 2). Overall, only three of nine patients completed treatment (33%) and none ceased for thrombocytopenia, although two of these patients required a temozolomide dose reduction.

Group C

There were twenty patients in the chemotherapy alone group (Group C), of which eight patients went on to complete twelve cycles of planned therapy (35%). Among the twelve patients who discontinued, seven patients did so due to disease progression, three patients due to clinical deterioration and two patients with thrombocytopenia. This translates to 25% grade 3-4 thrombocytopenia (Table 2). A total of two of twenty patients (10%) ceased secondary to thrombocytopenia. One patient developed this toxicity after cycle 1 and the other patient after cycle 4.

Factors associated with risk of toxicity and treatment discontinuation

Group A

We examined for the impact of extent of surgery, body surface area (BSA), creatinine clearance and total dose of temozolomide received on outcomes.

Specific characteristics of patients who required discontinuation due to thrombocytopenias in all groups are delineated (Table 3 and 4). Comparing patients in Group A who completed chemo-radiation phase versus patients who discontinued treatment, the only significant association was that those who failed to complete the full chemo-radiation treatment were more likely to be women (25% male and 75% female in Group A who discontinued ($p=0.012$)). There were no other significant difference in the two groups, with the median age being sixty-two years versus sixty-nine years respectively, median BSA was 1.89 versus 1.78, median creatinine clearance (mL/min) was ninety versus seventy, 82% received macroscopic debulking, 7% subtotal debulking and 11% biopsy only in Group A who completed treatment versus 50% macroscopic debulking, 13% subtotal debulking and 37% biopsy only in Group A who discontinued treatment ($p=0.17$) and the baseline haemoglobin(g/dL) was 13.8 versus 13.1, baseline neutrophils (mm³) was 7.4 versus 6.3 and baseline platelets (mm³) were 289 versus 363.

Comparing patients in Group A who completed their adjuvant chemotherapy course versus patients who discontinued treatment (Table 5), no significant associations were found. The median age was sixty years versus sixty-four years, 75% male and 25% female in Group A who completed treatment compared to 73% male and 27% female in Group A who discontinued ($p=0.89$), median body surface area (BSA) was 1.85 versus 1.93, median creatinine clearance (mL/min) was ninety versus eighty-two, 94% received macroscopic debulking, 0% subtotal debulking and 6% biopsy only in Group A who completed treatment versus 64% macroscopic debulking, 18% subtotal debulking and 18% biopsy only in Group A

who discontinued treatment ($p=0.11$) and the baseline haemoglobin(g/dL) was 13.9 versus 13.8, baseline neutrophils (mm³) was 7.0 versus 8.4 and baseline platelets (mm³) were 294 versus 257 (Table 4).

Group B

Comparing patients in Group B who completed chemo-radiation phase versus patients who discontinued treatment (Table 4), no significant correlations were found. The median age was sixty-eight years versus seventy-three years, 50% male and 50% female in Group B who completed treatment compared to 80% male and 20% female in Group B who discontinued ($p=0.34$), median body surface area (BSA) was 1.91 versus 1.89, median creatinine clearance (mL/min) was sixty-three versus seventy, 50% received macroscopic debulking, 0% subtotal debulking and 50% biopsy only in Group B who completed treatment versus 20% macroscopic debulking, 0% subtotal debulking and 80% biopsy only in Group B who discontinued treatment ($p=0.34$) and the baseline haemoglobin(g/dL) was 15.1 versus 14.4, baseline neutrophils (mm³) was 5.0 versus 9.3 and baseline platelets (mm³) were 235 versus 281 (Table 4).

Comparing patients in Group B who completed their adjuvant chemotherapy course versus patients who discontinued treatment (Table 5), no significant correlations were found. The median age was sixty years versus eighty-one years, 33% male and 67% female in Group B who completed treatment compared to 100% male and 0% female in Group B who discontinued ($p=0.25$), median body surface area (BSA) was 1.97 versus 1.81, median creatinine clearance (mL/min) was fifty-six versus seventy, 33% received macroscopic

debulking, 0% subtotal debulking and 67% biopsy only in Group B who completed treatment versus 100% macroscopic debulking, 0% subtotal debulking and 0% biopsy only in Group B who discontinued treatment ($p=0.25$) and the baseline haemoglobin(g/dL) was 15.2 versus 14.0, baseline neutrophils (mm³) was 2.7 versus 7.3 and baseline platelets (mm³) were 253 versus 157 (Table 4).

Group C

Comparing patients in Group C who completed their twelve cycles of chemotherapy versus patients who discontinued treatment (Table 5), the median age was sixty-four years versus thirty-six years, 25% male and 75% female in Group C who completed treatment compared to 42% male and 58% female in Group C who discontinued ($p=0.44$), median body surface area (BSA) was 1.86 versus 1.98, median creatinine clearance (mL/min) was eighty-nine versus seventy-eight, 88% received macroscopic debulking, 0% subtotal debulking and 12% biopsy only in Group C who completed treatment versus 33% macroscopic debulking, 0% subtotal debulking and 67% biopsy only in Group C who discontinued treatment ($p=0.017$) and the baseline haemoglobin(g/dL) was 14.3 versus 13.8, baseline neutrophils (mm³) was 4.9 versus 6.7 and baseline platelets (mm³) were 289 versus 218 (Table 4).

Efficacy data

The median overall survival in Group A is 13 months, Group B is 5 months and Group C is 11 months with a data censor of 1st January 2014.

Discussion

Post-operative chemo-radiotherapy as per the STUPP protocol in glioblastomas has demonstrated clinically meaningful survival benefits and has become rapidly adopted around the world (1-5). Less information is available about the tolerability of this regimen in the community setting where patients may not be as robust as those enrolled onto a clinical trial. Stupp *et al* (6) reported that only 37% of patients actually completed the full protocol whereas Gerber *et al* (7) have previously reported that 23% of patients completed the same protocol, slightly less than in the original phase three study. Importantly, they showed that some patients developed severe and fatal toxicities. More reassuringly, our study showed that 46% of patients were able to complete the full protocol, which is slightly higher than in the original study. Overall, that data suggests that levels of completion similar, or better, than those in the original phase three trial are possible. Also reassuringly, we found that rates of severe anemia and neutropenia were low and clinically easily managed.

In our study, 14% of patients in the full dose chemo-radiation group experienced grade 3-4 thrombocytopenia during the concurrent chemo-radiation phase. This is comparable to the rate of 15% observed by Gerber *et al* which is significantly higher than 3% events observed in the original Stupp *et al* publication. Stupp *et al* found that the majority of grade 3 and 4 thrombocytopenic complications amounting to 11% events arose from the adjuvant arm. Gerber *et al* similarly had a grade 3 and 4 thrombocytopenia rate of 4% events in the adjuvant arm. In our study however, we found no grade 3 and 4 thrombocytopenia during our adjuvant chemotherapy phase although 2 patients had to discontinue due to

grade 2 thrombocytopenia. Interestingly, we found that most of the thrombocytopenia we observed was during the chemo-radiation phase rather than the adjuvant phase of treatment. Furthermore, these thrombocytopenias were clinically relevant and associated with clinical harm. There were four deaths from complications as a result of their thrombocytopenias and one patient who survives with persisting significant pancytopenia.

Our analysis of clinical associations was only significant for women being more likely to experience significant thrombocytopenia and patients who experienced grade 5 toxicities (i.e. death) were women. This may be due to sex differences in pharmacokinetics and pharmacodynamics contributing to varying temozolomide plasma levels. There was perhaps a slight trend that patients with higher BSA always were at risk although this did not reach statistical significance. Armstrong *et al* reported that $BSA > 2.0$ in women is an independent predictor of myelotoxicity (8).

We also reviewed our cohort of patients for their concomitant medications and in particular anti-epileptic drugs, which patients with glioblastomas are commonly on. Only one out of nine patients experiencing grade 3-4 thrombocytopenia (Patient 4) in the chemo-radiation group was on an anti-epileptic agent, leviteracetam. Therefore, anti-epileptic drugs did not appear to correlate with severe thrombocytopenia.

Another hypothesis is that genetic or enzymatic deficiencies contribute to this increased toxicity. A prospective series of glioblastoma patients receiving full

dose chemo-radiotherapy and adjuvant chemotherapy found that methylated O6-methyl-guanine-DNA methyltransferase promoter and specific pleomorphic variants of the cytochrome P450 oxidoreductase and methionine adenosyltransferase 1A genes in plasma are independent predictors of thrombocytopenia (9). At this time, we are continuing to be more conservative with dosing in women, particularly with higher BSA and/or lower creatinine clearance.

We also provide data from the adjuvant phase of our abbreviated chemo-radiation group where 75% patients had grade 3-4 thrombocytopenia but no treatment cessation ensued. In our chemotherapy alone group, 25% experienced grade 3-4 thrombocytopenia resulting in a 10% discontinuation rate. Overall, we conclude that abbreviated chemo-radiation can be safely given and does not appear to have any increased toxicity compared to full dose STUPP with adequate patient selection.

Our study is limited as it is from a single tertiary institution and examines multiple groups of patients in a retrospective fashion. As a result, the number of patients in each group is small and hence identifying robust predictors of toxicity is difficult. Moreover, we did not include tumour genetic analysis, such as plasma methylated O6-methyl-guanine-DNA methyltransferase promoter, which could be a predictive factor of toxicity. Nevertheless this study remains one of very few studies to examine this important issue. It also expands the toxicity data available about the use of temozolomide in patients having abbreviated radiotherapy. A phase two study by Minniti *et al* found that concomitant short

course radiotherapy with temozolomide in an above seventy years of age population led to a median overall survival of 12.4 months and 15% combined rates of thrombocytopenia and neutropenia, not dissimilar to ours (10). Their group however had 100% completion rate likely due to the stringent inclusion and exclusion criteria of participating in a clinical trial.

Our study provides data about a similar approach in a non-trial setting within the community. In our study, we found that 20% of patients were selected for abbreviated treatment with a short-course chemo-radiation protocol and of these, the completion rate was much lower at 33%. Patients who received short-course chemo-radiation were significant older (median age seventy-three versus sixty-four years, $p=0.014$) and to only have had a biopsy (67% versus 33%, $p=0.011$). Interestingly, the reasons for discontinuation were progressive disease rather than treatment intolerance, with the observed 11% grade 3-4 thrombocytopenia events in the chemo-radiation arm which is slightly less than our full dose group, Group A.

Conclusion

In conclusion, our single institution experience confirms previous reports that Grade 3-4 thrombocytopenia is a significant problem in a small group of patients, predominantly women and having a higher BSA. In contrast, other forms of myelosuppression were rarely clinically significant. Interestingly, this was true between patients received full course chemo-radiation or abbreviated chemo-radiation. As some of the thrombocytopenic events were prolonged, occurred early in the STUPP protocol during chemo-radiation and could be fatal, more

work is required. Patients on treatment should be monitored carefully for this complication and appropriate supportive measures undertaken early to prevent catastrophic outcomes. Further work is required to identify predictive biomarkers for this rare but clinically significant problem.

References

1. Gan HK, Rosenthal MA, Cher L, Dally M, Drummond K, Murphy M, et al. Management of glioblastoma in Victoria, Australia (2006-2008). *Journal of Clinical Neuroscience*. 2015;22(9):1462-6.
2. Yabroff KR, Harlan L, Zeruto C, Abrams J, Mann B. Patterns of care and survival for patients with glioblastoma multiforme diagnosed during 2006. *Neuro-Oncol*. 2012;14(3):351-9.
3. Helseth R, Helseth E, Johannesen TB, Langberg CW, Lote K, Ronning P, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. *Acta Neurol Scand*. 2010;122(3):159-67.

4. Scoccianti S, Magrini SM, Ricardi U, Detti B, Buglione M, Sotti G, et al. Patterns of care and survival in a retrospective analysis of 1059 patients with glioblastoma multiforme treated between 2002 and 2007: a multicenter study by the Central Nervous System Study Group of Airo (italian Association of Radiation Oncology). *Neurosurgery*. 2010;67(2):446-58.
5. Bauchet L, Mathieu-Daude H, Fabbro-Peray P, Rigau V, Fabbro M, Chinot O, et al. Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. *Neuro-Oncol*. 2010;12(7):725-35.
6. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-96.
7. Gerber D, Grossman S, Zeltman M, Parisi M, Kleinberg L. The impact of thrombocytopenia from temozolamide and radiation in newly diagnosed adults with high-grade gliomas. *Neuro Oncol* (2007) 9 (1): 47-52.
8. Armstrong T, Cao Y, Scheurer M et al. Risk analysis of severe myelotoxicity with temozolamide: The effects of clinical and genetic factors. *Neuro Oncol* (2009) 11(6): 825-32.
9. Lombardi G, Rumiato E, Bertorelle R, Saggioro D, Farina P, Puppa AD et al. Clinical and Genetic Factors Associated With Severe Hematological Toxicity in Glioblastoma Patients During Radiation Plus Temozolomide Treatment: A Prospective Study. *Am J Clin Oncol* (2015);38(5):514-9..
10. Minniti G, Lanzetta G, Scaringi C, Caporello P, Salvati M, De Sanctis V, Giangaspero F, Enrici RM. Phase II study of short-course radiotherapy plus

concomitant and adjuvant temozolamide in elderly patients with glioblastoma.

Int J Radiat Oncol Bio Phys. 2012;1;83(1):93-9.

Table 1: Baseline characteristics of patients

	All patients	Full dose CRT (Group A)	Partial dose CRT (Group B)	P-value*	Chemotherapy alone (Group C)
Median age (years)	57 (32-81)	64 (41-77)	73 (43-81)	P=0.014	52 (32-74)
Gender				P=0.83	
Male	35 (55%)	22 (63%)	6 (67%)		7 (35%)
Female	29 (45%)	13 (37%)	3 (33%)		13 (65%)
Ethnic Origin				P=0.46	
Anglo-Saxons	42 (66%)	24 (69%)	5 (56%)		13 (65%)
Eastern European	16 (25%)	9 (26%)	4 (44%)		3 (15%)
Asian	6 (9%)	2 (5%)	0 (0%)		4 (20%)
Tumour grade at diagnosis				P=0.57	
Grade 4	52 (81%)	33 (94%)	8 (89%)		11 (55%)
Grade 3	12 (19%)	2 (6%)	1 (11%)		9 (45%)
Tumour laterality				P=0.25	
Right	33 (52%)	16 (46%)	6 (67%)		11 (55%)
Left	28 (44%)	17 (49%)	2 (22%)		9 (45%)
Bilateral	3 (4%)	2 (5%)	1 (11%)		0 (0%)

Tumour position				P=0.86	
Frontal	23 (36%)	13 (37%)	3 (33%)		7 (35%)
Parietal	12 (19%)	8 (23%)	3 (33%)		1 (5%)
Temporal	10 (16%)	7 (20%)	2 (22%)		1 (5%)
Occipital	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Cerebellar	1 (1%)	0 (0%)	0 (0%)		1 (5%)
Others (>1 lobe)	18 (28%)	7 (20%)	1 (11%)		10 (50%)
Surgery				P=0.011	
Macroscopic debulking	40 (63%)	26 (74%)	3 (33%)		11 (55%)
Partial debulking	3 (4%)	3 (9%)	0 (0%)		0 (0%)
Biopsy only	21 (33%)	6 (17%)	6 (67%)		9 (45%)
Baseline haematology, median				N/A	
Haemoglobin (g/dL)	13.9	13.8	14.7		14.0
Neutrophils (/mm ³)	6800	7100	8500		6550
Platelets (/mm ³)	272	294	253		226

* For comparison between full course versus short course chemo-RT

Table 2: Toxicities by CT CAE V4.0 grading

	Group A		Group B		Group C
	Full dose CRT N=35	Adjuvant Chemo N=27	Partial dose CRT N=9	Adjuvant Chemo N=4	Chemo Alone N=20
Haemoglobin					
Grade 1	3 (9%)	3 (11%)	0 (0%)	0 (0%)	6 (30%)
Grade 2	4 (11%)	1 (4%)	0 (0%)	1 (25%)	3 (15%)
Grade 3	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutrophils					
Grade 1	3 (9%)	1 (4%)	1 (11%)	1 (25%)	3 (15%)
Grade 2	1 (3%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)
Grade 3	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Grade 4	3 (9%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Platelets					
Grade 1	6 (17%)	10 (37%)	2 (22%)	1 (25%)	7 (35%)
Grade 2	1 (3%)	2 (7%)	0 (0%)	0 (0%)	2 (10%)
Grade 3	0 (0%)	0 (0%)	0 (0%)	3 (75%)	2 (10%)
Grade 4	5 (14%)	0 (0%)	1 (11%)	0 (0%)	3 (15%)
Patients Discontinuing For Thrombocytopenia	5 (14%)	1 (4%)	1 (11%)	0 (0%)	2 (10%)

Table 3: Clinical characteristics of patients discontinuing chemo-radiation, not proceeding to adjuvant chemotherapy and patients discontinuing adjuvant chemotherapy and chemotherapy alone secondary to thrombocytopenia

	Age (years)	Gender	Surgery	Body surface area (m ²)	Total Dose TMZ (mg)	CrCl (mL/min)	Individual outcomes
Patient 1	70	M	Macroscopic Resection	1.82	5880 (100%)	74	Had 2 nd line bevacizumab and died 6 months post CRT from disease
Patient 2	73	F	Macroscopic Resection	1.82	5880 (100%)	71	Prolonged hospitalization with thrombocytopenia and subsequently died from disease
Patient 3	68	F	Macroscopic Resection	1.53	3920 (100%)	45	Prolonged hospitalization with thrombocytopenia and subsequently died from pneumonia
Patient 4	69	F	Macroscopic Resection	1.78	3940 (67%)	56	Died from severe sepsis after profound thrombocytopenia and prolonged hospital admission
Patient 5	52	F	Partial Resection	1.78	5250 (100%)	68	Still alive. Remains profoundly pancytopenic.
Patient 6	68	F	Biopsy	1.65	2800 (100%)	90	Prolonged hospitalization with thrombocytopenia and subsequently died from disease
Patient 7	65	F	Biopsy	2.03	3000 (50%)	60	Received 2 nd line chemotherapy and subsequently died from disease 8 months later
Patient 8	34	F	Biopsy	2.01	1500 (6%)	90	Severe thrombocytopenia and concurrent clinical deterioration and died from disease
Patient 9	43	F	Biopsy	1.97	9300 (40%)	88	Severe thrombocytopenia and prolonged hospitalization and died from disease progression

Patients 1-5 – full dose chemo-radiation group part 1

Patient 6 - abbreviated dose radiation group part 1

Patient 7 – full dose chemo-radiation group part 2 (adjuvant phase)

Patients 8 - 9 – chemotherapy alone group

Table 4: Characteristics of patients in full dose and partial dose chemo-radiation groups

	Full dose CRT completed N=27	Full dose CRT discontinued N=8	P-value	Partial dose CRT completed N=4	Partial dose CRT discontinued N=5	P-value
Median age (years)	62 (45-76)	69 (53-77)	P=0.12	68 (43-81)	73 (68-78)	P=0.31
Gender			P=0.012			P=0.34
M	20 (74%)	2 (25%)		2 (50%)	4 (80%)	
F	7 (26%)	6 (75%)		2 (50%)	1 (20%)	
Median BSA	1.89	1.78	P=0.12	1.91	1.89	P=0.83
Median CrCl ml/min	90	70	P=0.04	63	70	P=0.39
Surgery			P=0.17			P=0.34
Macroscopic debulking	22 (82%)	4 (50%)		2 (50%)	1 (20%)	
Subtotal debulking	2 (7%)	1 (13%)		0 (0%)	0 (0%)	
Biopsy only	3 (11%)	3 (37%)		2 (50%)	4 (80%)	
Total dose TMZ (%)	96.9	95.9	P=0.82	100	78.6	P=0.19
Baseline haem median			N/A			N/A
Hb (g/dL)	13.8	13.1		15.1	14.4	
Neut (/mm ³)	7.4	6.3		5.0	9.3	
Plt (/mm ³)	289	363		235	281	

Table 5: Characteristics of patients in adjuvant phase of full dose and partial dose chemo-radiation and palliative chemotherapy for recurrence only groups

	Adjuvant phase full dose CRT completed N=16	Adjuvant phase full dose CRT discontinued N=11	P-value	Adjuvant phase partial dose CRT completed N=3	Adjuvant phase partial dose CRT discontinued N=1	P-value	Palliative chemo alone completed N=8	Palliative chemo alone discontinued N=12	P-value
Median age (years)	60 (41-74)	64(44-71)	P=0.83	60 (43-75)	81 (81)	P=0.60	64 (55-74)	36 (32-71)	P=0.10
Gender M F	12 (75%) 4 (25%)	8 (73%) 3 (27%)	P=0.89	1 (33%) 2 (67%)	1 (100%) 0 (0%)	P=0.25	2 (25%) 6 (75%)	5 (42%) 7 (58%)	P=0.44
Median BSA	1.85	1.93	P=0.48	1.97	1.81	P=0.48	1.86	1.98	P=0.38
Median CrCl ml/min	90	82	P=0.40	56	70	P=0.41	89	78	P=0.06
Surgery Macroscopic debulking Subtotal debulking Biopsy only	15 (94%) 0 (0%) 1 (6%)	7 (64%) 2 (18%) 2 (18%)	P=0.11	1 (33%) 0 (0%) 2 (67%)	1 (100%) 0 (0%) 0 (0%)	P=0.25	7 (88%) 0 (0%) 1 (12%)	4 (33%) 0 (0%) 8 (67%)	P=0.017
Total dose TMZ (%)	97.5	49.8	P=0.0001	93.3	17.0	P=0.004	100	31.3	P=0.0001
Baseline haem, median			N/A			N/A			N/A

Hb (g/dL)	13.9	13.8		152	140		143	138	
Neut (/mm3)	7	8.4		2.7	7.3		4.9	6.7	
Plt (/mm3)	294	257		253	157		289	218	

Figure 1: Flow Chart of patients reviewed and their progression through post-operative treatment

Title

Clinical correlates of severe thrombocytopenia from temozolomide in glioblastoma patients

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