



Adjuvant chemotherapy after severe myelotoxicity during chemoradiation phase in malignant gliomas. Is it feasible? Results from AINO study (Italian Association for Neuro-Oncology)

Veronica Villani¹ · Elena Anghileri² · Luca Prosperini³ · Giuseppe Lombardi⁴ · Roberta Rudà⁵ · Paola Gaviani⁶ · Simona Rizzato⁷ · Gaetano Lanzetta^{8,11} · Alessandra Fabi⁹ · Claudia Scaringi¹⁰ · Edoardo Pronello⁵ · Giorgia Simonetti⁶ · Giada Targato⁷ · Andrea Pace¹

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Abstract

Background Malignant gliomas (MG) are aggressive brain tumours in adults. The standard of care is concurrent radiation plus temozolomide (TMZ) [chemo-radiotherapy (CRT)] followed by TMZ maintenance up to 6 months. TMZ is considered to have a low toxicity profile, but several studies reported occurrence of severe myelosuppression, especially during the concomitant phase. Toxicity may be prolonged, thus treatment should be discontinued.

Purpose To evaluate the risk of recurrent myelotoxicity during adjuvant chemotherapy (CT) in patients who recovered from severe myelotoxicity during CRT.

Methods We retrospectively collected data on patients with MG who developed and recovered from severe myelotoxicity during CRT from eight Italian neuro-oncology centers.

Results We included 87 patients. Histology was Glioblastoma (GBM) in 78 patients (89.7%); 60% of patients were female. After myelotoxicity recovery, 54 (62%) received treatment. The majority of them (82%, $n = 44$) received adjuvant TMZ and 18% ($n = 10$) others treatments. Out of 44 patients who received adjuvant TMZ, 34% experienced the re-occurrence of grade 3–4 myelotoxicity which required permanent CT discontinuation in 6 (13%) cases. Patients who received TMZ or other treatments had longer overall (OS) (adjusted HR 0.46, $p = 0.008$) and progression free survival (PFS) (adjusted HR 0.57, $p = 0.034$) than those who remained untreated.

Conclusion Our study suggests that after severe myelotoxicity the majority of patients received treatment, particularly with TMZ. Only a fraction of patients experienced toxicity recurrence, suggesting that TMZ is well tolerated and had an impact on PFS and OS.

Keywords Malignant glioma (MG) · Hematological toxicity · Concomitant chemo-radiotherapy (CRT) · Adjuvant chemotherapy (CT) · Temozolomide (TMZ)

Introduction

Malignant gliomas (MG) are the most common and aggressive forms of primary brain tumours in adults.

Today, the standard of care is surgery, followed by concomitant Temozolomide (TMZ) with radiation therapy (CRT), and adjuvant TMZ [1]. Stupp et al. [1] reported that the treatment was reasonably well tolerated as 85% of

participants completed the full course of CRT as planned. However, only 47% of patients completed the planned six cycles of adjuvant TMZ, and 8% discontinued due to myelotoxicity. TMZ is considered to be a safe drug; however, several case reports and small series studies have reported severe myelotoxicity occurring during CRT or adjuvant TMZ [2].

In Stupp trial, the main toxicity was grade 3–4 thrombocytopenia, and occurred in 3% of patients during the CRT and 11% of patients during adjuvant chemotherapy (CT), respectively [1].

Gerber et al. [3] in a single-centre study reported severe myelosuppression in a minority of patients: 19% of patients

✉ Veronica Villani
veronica.villani@ifg.it

Extended author information available on the last page of the article

experienced grade 3–4 thrombocytopenia (80% of these occurring during the CRT and 20% during the adjuvant CT), with a median duration of 32 days. Two patients (4%) presented prolonged thrombocytopenia and one died from this complication. A systematic review of the literature [2] showed that severe myelotoxicity mainly occurred during CRT. The myelotoxicity ranged from few weeks till more than 1 year [4, 5] and patients did not receive adjuvant TMZ, because they were considered at risk of new severe toxicity.

Risk factors related to haematological toxicity include clinical parameter as gender, Body Surface Area (BSA), Body Mass Index (BMI), taking steroids, pretreatment platelet count, methylation status of the (O 6-methyl-guanine–DNA methyl-transferase) MGMT promoter on peripheral mononuclear cells, some specific MGMT polymorphisms and other epigenetic mechanism as single CpG methylation of HSBP2s [5–16].

Despite this approach, glioblastoma (GBM) is associated with a poor median overall survival of less than 24 months and relapse is inevitable [1, 17].

However, little data are available about the haematological toxicity recurrence during adjuvant CT in glioma patients who experienced severe haematological toxicity during CRT.

The aim of our retrospective multicentric AINO (Italian Association for Neuro-Oncology) study was to analyse the incidence of second haematological toxicity during adjuvant CT in patients with MG who recovered after severe haematological toxicity during CRT.

Methods

We retrospectively collected data of patients with MG who developed grade 3 or 4 (as the National Cancer Institute (NCI) Common Toxicity criteria (NCICT-CAE) version 3.0 [18]) myelotoxicity during CRT and recovered, from January 2007 to December 2019. The AINO multicentre study included eight Italian neuro-oncology centers. We excluded patients who did not resolve toxicity, who died. Following institutional review board approval, we reviewed demographics, clinical–radiological data [including Karnofsky Performance Scale (KPS) and surgical exeresis extension], histopathological diagnosis and therapy details of all patients. Data on the reason of treatment discontinuation were also collected.

In cases with an adequate amount of tissue, IDH1 was detected [immunochemistry using anti-IDH1 (R132H) or Next Generation sequencing analyses] and MGMT promoter methylation status analyzed as common current practice [Methylation-Specific PCR (PCR) or pyrosequencing].

Myelotoxicity data included: type, onset time and duration, eventually use of growth factors as Granulocyte

Colony-Stimulating Factor (G-CSF) and blood/platelet transfusions. For patients treated with adjuvant treatment, we considered type, severity of toxicity, time to progression and reasons for discontinuation. Outcome, including progression-free survival (PFS) and overall survival (OS) were available for all patients.

Statistical analysis

Data are expressed as count (proportion) and as a mean (standard deviation) or median (range), where appropriate. Differences were tested by the Fisher Exact test for categorical variables and by the Mann–Whitney *U* test for continuous variables.

Survival analyses with Kaplan–Meier curves and proportional hazard Cox regression models explored OS and PFS in patients who started adjuvant chemotherapy versus those who did not. Demographic and clinical variables were also entered in the multivariable Cox models to explore whether there were factors other than adjuvant chemotherapy associated with better or worse prognosis.

Two-sided *p* values less than 0.05 were considered significant.

Results

We identified 87 patients (34 men, 53 women) with a mean age of 58.4 (10.8) years who were diagnosed with GBM ($n = 78$) or any other MG ($n = 9$). Patients' baseline characteristics are shown in Table 1.

Forty-one patients developed grade 3 (47.1%) or 46 grade 4 (52.9%) myelotoxicity after a median time of 4 weeks (range 2–10) since starting CRT. The resolution of myelotoxicity was observed within a median time of 6 weeks (range 1–80).

Thirty-five patients (40.2%) had 1 blood-cell lineages deficiency; 29 (33.3%) had 2 blood-cell lineages, and 23 (26.5%) had more than 2 blood-cell lineages deficit (see Table 2). Regarding one blood-cell lineages deficiency, the majority of patients presented isolated thrombocytopenia ($n = 23$, 65.7%), followed by lymphopenia ($n = 7$, 20%) and neutropenia ($n = 5$, 14.3%). We found no association of grade or type of myelotoxicity with age, KPS, histology, radiotherapy dose, MGMT promoter methylation and IDH-1 status (all *p* values > 0.12). The onset of myelotoxicity was significantly shorter in patients who developed grade 4 myelotoxicity respect to those who developed grade 3 toxicity (4.4 ± 1.5 versus 5.4 ± 1.5 weeks, $p = 0.001$), but there was no difference in terms of duration of toxicity ($p = 0.65$). One blood-cell-type deficiency occurred later and lasted shorter than two or more blood-cell lineages reductions, as shown in Fig. 1. Administration of G-CSF and/or blood

Table 1 Baseline characteristics of patients who developed severe myelotoxicity ($n=87$)

Sex	
Female	53 (60.9)
Male	34 (39.1)
Age, years	
Mean (SD)	58.4 (10.8)
Median (range)	60 (16–78)
KPS	
Mean (SD)	88.3 (11.3)
Median (range)	90 (50–100)
> 70	77 (88.5)
≤ 70	10 (11.5)
Surgery	
Biopsy/partial	35 (40.2)
Gross/total	52 (59.8)
Histology	
GBM	78 (89.7)
Any MG out of GBM	9 (10.3)
MGMT promoter methylation status	
Not methylated	34 (39.1)
Methylated	33 (37.9)
Not available	20 (23.0)
IDH-1	
Wild type	40 (46.0)
Mutation	16 (18.4)
Not available	31 (35.6)
Radiotherapy dose	
60 Gy	80 (92.0)
54 Gy	7 (8.0)

GBM glioblastoma, IDH-1 Isocitrate dehydrogenase 1, KPS Karnofsky Performance Score, MGMT O⁶-methylguanine-DNA methyltransferase (MGMT), Gy Gray, SD standard deviation

or platelet transfusion were required in 32 (36.7%) and 49 (56%) patients, respectively. No major complications related to myelotoxicity as infection or haemorrhage were observed.

Myelotoxicity after starting adjuvant chemotherapy

After myelotoxicity resolution, 33 (38%) patients did not receive treatments, whereas 54 (62.1%) patients received therapy (Fig. 2): TMZ 150–200 mg/m²/day ($n=44$), metronomic TMZ schedules ($n=4$), lomustine ($n=3$), bevacizumab ($n=2$), tamoxifene ($n=1$).

There were no demographic or clinical differences between the two groups (treatments vs. no treatment), including the type and grade of myelotoxicity, except for better KPS at diagnosis ($p=0.046$) and after CRT ($p=0.003$) in those who did further treatment as compared with those who did not (see also Table 3).

Out of 54 patients who received another therapy after CRT, 21 (38.9%) experienced recurrent grade 3 or 4 myelotoxicity, including isolated thrombocytopenia or neutropenia or lymphopenia ($n=16$) and co-occurring thrombocytopenia or neutropenia or lymphopenia ($n=5$). Of them, 15/44 (34%) were treated with adjuvant TMZ and 6/10 (60%) treated with other treatments ($p=0.16$).

We observed no demographic and clinical differences between patients with ($n=21$) and without ($n=33$) recurrent myelotoxicity, including type, grade, time of onset and time to resolution of the post-CRT toxicity. These data did not change even after limiting the analysis only to the 44 patients treated with adjuvant TMZ.

Fewer patients treated with adjuvant TMZ ($n=6/44$) discontinued the treatment due to toxicity as compared with other therapies ($n=5/10$) ($p=0.021$). None of them needed G-CSF or blood/platelet transfusion for any blood type deficiency. No major complication related to myelotoxicity was observed.

Outcomes (OS and PFS) after starting adjuvant chemotherapy

Patients who received adjuvant TMZ or other treatments ($n=54$) had longer OS (adjusted HR 0.46, $p=0.008$) and PFS (adjusted HR 0.57, $p=0.034$) than those who remained untreated ($n=33$) following resolution of CRT-related myelotoxicity (see also Fig. 3a, b). These data did not change substantially even after limiting the analysis only to adjuvant TMZ 5/28 ($n=44$) vs. no treatment ($n=33$): adjusted HR for OS = 0.52 ($p=0.025$) and adjusted HR for PFS = 0.62 ($p=0.065$).

Moreover, patients diagnosed with any MG different from GBM had a reduced risk of death (adjusted HR 0.17, $p=0.016$) and of disease progression (adjusted HR 0.27, $p=0.007$) than those with GBM (see also Tables 4, 5).

The MGMT promoter methylation status and IDH1 mutation status did not affect both the OS and PFS, possibly because of the reduced sample size (data on MGMT and on IDH1 status were available only for 67 and 56 patients, respectively).

Predictor factors for iatrogenic myelotoxicity

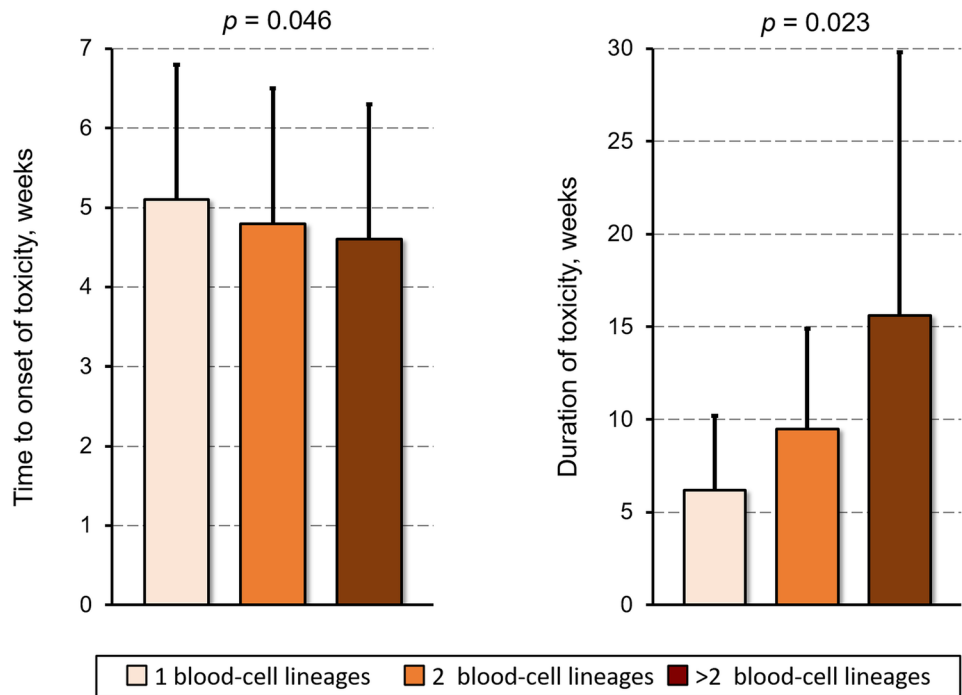
We performed an additional retrospectively analysis to identify the potential predictors for iatrogenic myelotoxicity. For this reason we identified a control group in the Neuro-Oncology Unit's database of Regina Elena, collecting 1500 primary brain tumors. From these 1500 patients, we only selected those glioma patients, from January 2007 to December 2019, who did not experience myelotoxicity during CRT. We considered 456 MG patients. We then compared the clinical and histo-molecular variables

Table 2 Grade 3 or 4 myelotoxicity in patients treated with radiotherapy plus concomitant temozolomide ($n = 87$)

	1 blood-cell line- age deficit	2 blood-cell line- ages deficit	> 2 blood-cell line- ages deficit	Total
<i>N</i> (%)	35 (40.2)	29 (33.3)	23 (26.5)	87 (100)
Toxicity Grade according to CTCAE, <i>n</i> (%)				
3	27 (65.9)	12 (29.2)	2 (4.9)	41 (100)
4	8 (17.4)	17 (37.0)	21 (45.6)	46 (100)
Thrombocytopenia, <i>n</i> (%)	23 (65.7)	27 (50)	23 (25)	-
Lymphopenia, <i>n</i> (%)	7 (20.0)	17 (31.4)	23 (25)	
Neutropenia, <i>n</i> (%)	5 (14.3)	10 (18.6)	23 (25)	
Anemia, <i>n</i> (%)	0	0	23 (25)	
Tot <i>N</i> (%) any grade 3 or 4 AE	35 (100)	54 (100)	92 (100)	
Time to onset of toxicity, weeks				
Mean (SD)	5.1 (1.7)	4.8 (1.1)	4.6 (1.7)	4.9 (1.5)
Median (range)	5 (1–8)	4 (3–7)	4 (3–10)	4 (1–10)
Duration of toxicity, weeks				
Mean (SD)	6.2 (4.0)	9.5 (5.4)	15.6 (14.5)	9.4 (8.8)
Median (range)	6 (1–23)	8 (2–20)	8 (2–80)	6 (1–80)
Administration of G-CSF	5 (15.6)	8 (25.0)	19 (59.4)	32 (100)
Blood or platelet transfusion	7 (14.3)	22 (44.9)	20 (40.8)	49 (100)

CTCAE Common Terminology Criteria for Adverse Events, G-CSF Granulocyte Colony-Stimulating Factor, SD standard deviation

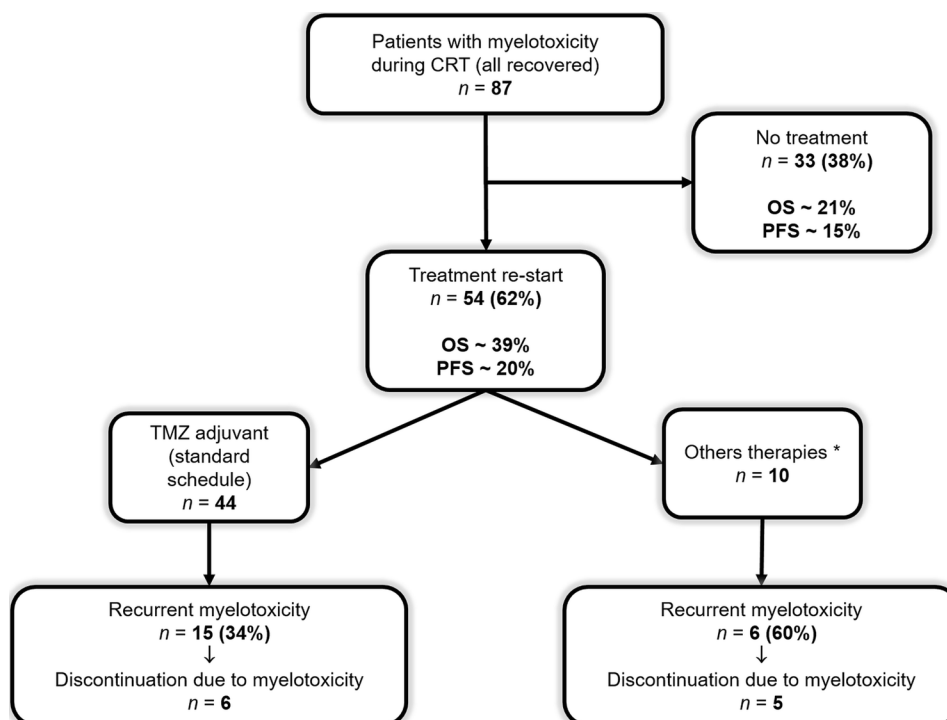
Fig. 1 Time of onset and time to resolution of CRT-related myelotoxicity according to the number of involved blood-cell lineages



between the study cohort ($n = 87$) to control cohort ($n = 456$). We observed that female sex ($p < 0.001$), age ($p = 0.01$), histology ($p = 0.001$) and IDH-1 ($p = 0.041$) are predictors factors at baseline for myelotoxicity (see Table 6). Lastly, we estimated no difference between

patients who developed myelotoxicity and those who did not in terms of PFS and OS (data not shown).

Fig. 2 Flowchart of patient disposition



Discussion

Our study suggests that starting adjuvant CT or another therapy after resolution of CRT-related myelotoxicity results in longer OS and PFS and in a relatively small risk of recurrent myelotoxicity, especially with adjuvant TMZ.

TMZ treatment has been considered to have a low toxicity profile, as reported by Stupp et al. and other different studies reported an overall incidence of 5–8% for grade 3 or 4 myelotoxicity [1, 7, 8]. Niewald et al. [19] reported high rates of myelotoxicity with discontinued treatment in 50% of GBM treated with CRT.

Subsequent studies showed that severe myelotoxicity could be even higher during CRT compared with adjuvant. Today, there are no guidelines about how to treat patients with glioma after remission of severe myelotoxicity during CRT. However, given the lack of clear evidence, in clinical practice, patients may or not receive adjuvant CT after remission of their myelotoxicity on the basis of single-centre case by case evaluation of the risk.

In this multicentre retrospective study, we observed that the majority of patients that recovered from CRT-induced severe myelotoxicity are largely treated with adjuvant CT (61.6%), and only 38.4% patients did not receive any treatment.

There were not significant clinical differences between the two groups. However, considerable caution is required in interpreting such data due to the design of the present study. Among the treated patients, the most

received standard adjuvant TMZ where 34% experienced myelotoxicity re-occurrence, but only 13% discontinued adjuvant TMZ for this reason.

In previous data, patients that develop prolonged severe myelosuppression during CRT usually did not receive CT for high risk of recurrence of severe toxicity [2]. Lombardi et al. [5] observed that all patients discontinuing TMZ during the concomitant phase for severe haematological toxicity did not receive adjuvant treatment. Gerber et al. [3] concluded that around 20% of patients with newly diagnosed MG receiving TMZ are at risk of severe thrombocytopenia, and half of them with risk of sustained, prolonged and potentially irreversible toxicity.

Lin et al. [20] analysed the impact of concurrent versus adjuvant CT on the severity of lymphopenia in gliomas and showed that CRT appears to be the dominant contributor to the severity of acute lymphopenia.

An analysis on 3400 patients concluded that the hematologic toxicity due to TMZ represent a significant concern and the mechanisms involved could be different from the other alkylants [14].

During the CRT, our patients with myelotoxicity initially reported one blood-cell lineages, and later deficiencies involving more than one blood-cell lineages as thrombocytopenia and neutropenia or thrombocytopenia, neutropenia and anaemia. During adjuvant CT phase, we observed only cases of isolated thrombocytopenia or neutropenia or lymphopenia.

Table 3 Differences between patients who did CT treatment (treatment) and those who did not (no treatment), after recovery from CRT myelotoxicity ($n = 87$)

	Treatment ($n = 54$)	No treatment ($n = 33$)	<i>p</i> value
Sex			
Female	33 (61.1)	20 (60.6)	0.90
Male	21 (38.9)	13 (39.4)	
Age, years			
Mean (SD)	57.6 (10.7)	59.8 (10.8)	0.31
KPS at diagnosis			
Mean (SD)	90.0 (11.2)	85.4 (11.2)	0.045
KPS post-CRT			
Mean (SD)	86.7 (13.2)	78.5 (12.5)	0.003
Surgery			
Biopsy/partial	20 (37.0)	15 (45.5)	0.50
Gross/total	34 (63.0)	18 (54.5)	
Histology			
GBM	49 (90.7)	29 (87.9)	0.72
Any MG out of GBM	5 (9.3)	4 (12.1)	
MGMT promoter			
Not methylated	24 (44.4)	10 (30.3)	0.61
Methylated	21 (38.9)	12 (36.4)	
Not available	9 (16.7)	11 (33.3)	
IDH-1			
Wild type	26 (48.1)	14 (42.4)	0.34
Mutation	13 (24.1)	3 (9.1)	
Not available	15 (27.8)	16 (48.5)	
Radiotherapy dose			
60 Gy	48 (88.9)	32 (97)	0.25
54 Gy	6 (11.1)	1 (3)	
Hematological toxicity during CRT			
Grade 3	28 (51.9)	13 (39.4)	0.33
Grade 4	26 (48.1)	20 (60.6)	
1 blood-cell lineage	25 (46.3)	10 (30.3)	0.28
2 blood-cell lineage	16 (29.6)	13 (39.4)	
> 2 blood-cell lineage	13 (24.1)	10 (30.3)	

CRT ChemoRadio Therapy, GBM glioblastoma, IDH-1 isocitrate dehydrogenase 1; KPS Karnofsky Performance Score, MGMT O⁶-methylguanine-DNA methyl-transferase, SD standard deviation

Our data are in line with the literature, suggesting that thrombocytopenia is the first sign of severe myelosuppression [3–5].

In our study, the median time of myelotoxicity occurrence during CRT was 4 weeks (range 1–10) with a median time of 6 (range 1–80) weeks for resolution. Gerber et al. [3] reported that the median onset was on day 52 of therapy.

In addition, some of the above-mentioned risk factors of myelotoxicity as clinical factors and epigenetic profile, also the use of antiepileptic drugs (AED) may have an impact [13, 15, 16]. Given the absence of a control group of patients who did not develop myelotoxicity, we cannot confirm any reported associations between toxicity and the use of AED or MGMT methylation status.

The main goal of our study was to assess the risk of myelotoxicity induced by adjuvant CT in patients recovered by previous severe myelotoxicity during CRT of Stupp regimen. The results of this study show that the majority of patients received treatment, in particular TMZ, and may be safely concluded in the majority of them.

Moreover, patients treated with adjuvant CT showed a positive outcome trend; nevertheless, such data need to be confirmed in larger prospective studies. To our knowledge, survival advantage in patients that did not experience pancytopenia have been reported in few small studies [21–24]. The reasons for the positive correlation between leukopenia/thrombocytopenia and positive outcome have also been hypothesized, and need to be proved. Firstly, it remains unclear whether patients who do not show a notable

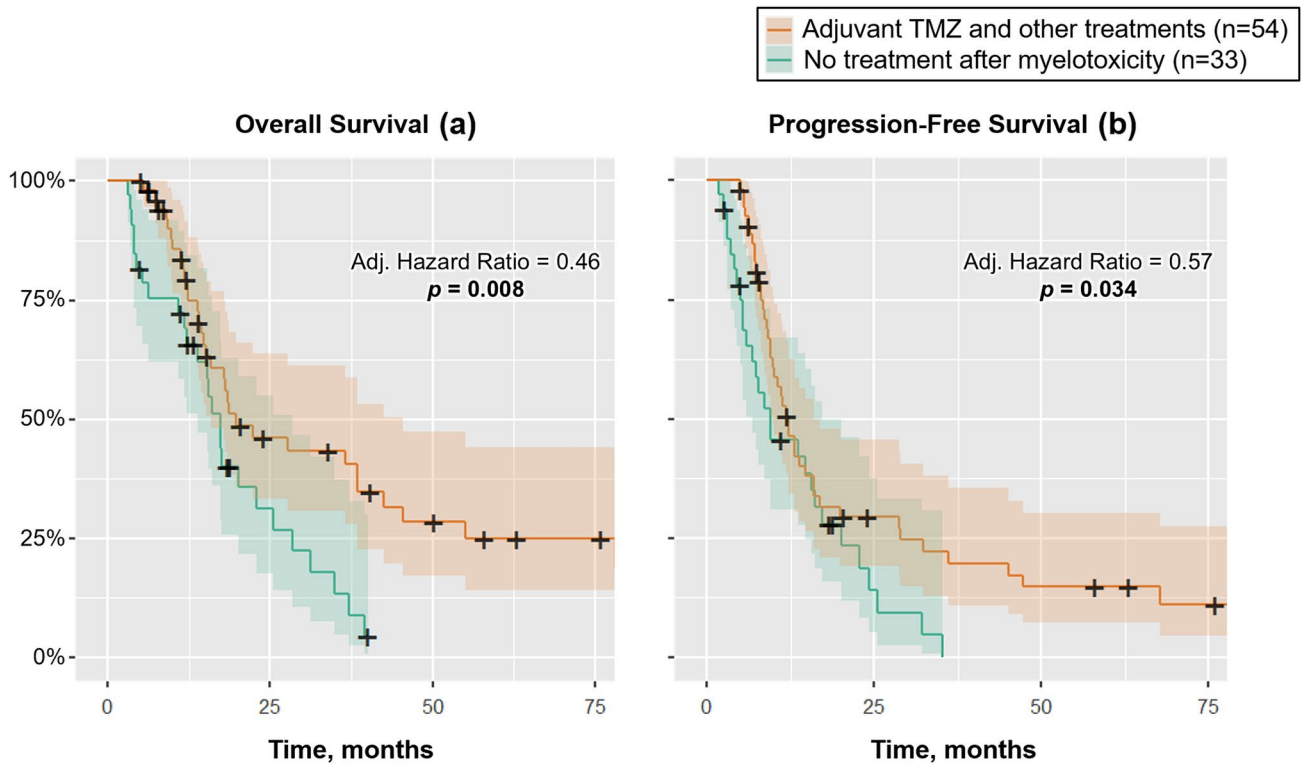


Fig. 3 Survival analysis **a** overall survival (OS) and **b** progression-free survival (PFS) according to treatment strategy after resolution of CRT-related myelotoxicity

Table 4 Cox proportional hazard models predicting overall survival (dependent variable) by clinical characteristics, molecular markers and adjuvant treatment in patients with severe myelotoxicity ($n = 87$)

	Univariate analysis			Multivariate analysis		
	HR	95% CIs	<i>p</i>	HR	95% CIs	<i>p</i>
Sex (male vs. female)	0.92	0.54–1.57	0.76			
Age (each year)	1.01	0.98–1.03	0.55			
KPS (> 70 vs. ≤ 70)	0.72	0.32–1.59	0.41			
Surgery (gross/total vs. partial/biopsy)	0.62	0.37–1.05	0.08			
Histology (any MG out of GBM vs. GBM)	0.19	0.05–0.76	0.020	0.17	0.04–0.72	0.016
MGMT (methylated vs. unmethylated) *	0.74	0.40–1.39	0.35			
IDH-1 (mutated vs. wild-type) **	0.64	0.27–1.49	0.64			
adjuvant chemotherapy (yes vs. no)	0.49	0.29–0.85	0.011	0.46	0.26–0.82	0.008

GBM glioblastoma, *KPS* Karnofsky Performance Score, *IDH-1* isocitrate dehydrogenase 1, *MGMT* O⁶-methylguanine-DNA methyl-transferase

*Available only for 67 patients; **available only for 56 patients

decrease in blood counts in response to TMZ are treated below therapeutic range. Second, leukopenia could be a positive prognostic factor in relation to the knowledge that neutrophil exhibit a pro-tumorigenic activity [25]. Besides, induced-bone marrow failure can include also reduction of bone marrow-derived cells (BMDC), endothelial Precursor Cell (EPC) and myeloid-derived suppressor cells (MDSC),

all cell populations essential for MG development and progression [26, 27].

The present study is not exempt from limitations, mainly due to its retrospective-real life design and small sample size. Even if database plan was discussed and defined by reaching an agreement on the minimum dataset to be analysed by a devoted network, we still cannot exclude a certain degree of inter-centre variability. Despite these limitations,

Table 5 Cox proportional hazard models predicting progression-free survival (dependent variable) by clinical characteristics, molecular markers and adjuvant treatment in patients with severe myelotoxicity ($n=87$)

	Univariate analysis			Multivariate analysis		
	HR	95% CIs	<i>p</i>	HR	95% CIs	<i>p</i>
Sex (male vs. female)	1.15	0.71–1.86	0.56			
Age (each year)	1.01	0.99–1.04	0.38			
KPS (> 70 vs. ≤ 70)	0.72	0.36–1.46	0.37			
Surgery (partial/biopsy vs. gross/total)	0.62	0.43–1.10	0.12			
Histology (any MG out of GBM vs. GBM)	0.31	0.13–0.79	0.013	0.27	0.11–0.70	0.007
MGMT promoter (methylated vs. unmethylated) *	0.71	0.41–1.23	0.22			
IDH-1 (mutated vs. wild-type) **	0.62	0.30–1.27	0.19			
Adjuvant chemotherapy (yes vs. no)	0.61	0.37–0.99	0.046	0.57	0.34–0.96	0.034

GBM glioblastoma, KPS Karnofsky Performance Score, IDH-1 isocitrate dehydrogenase 1, MG malignant Glioma, MGMT O⁶-methylguanine-DNA methyl-transferase

*Available only for 66 patients; ** available only for 55 patients

Table 6 Baseline differences between patients who developed myelotoxicity (present study) ($n=87$) and a control cohort of consecutive patients without myelotoxicity ($n=456$)

	Present study, $n=87$ (100%)	Control cohort, $n=456$ (100%)	<i>p</i> value
Sex			
Female	53 (60.9)	156 (34.2)	<0.001
Male	34 (39.1)	300 (65.8)	
Age, years			
Mean (SD)	58.4 (10.8)	54.8 (13.1)	0.01
Median (range)	60 (16–78)	56 (19–85)	
KPS			
> 70	77 (88.5)	412 (90.4)	0.56
≤ 70	10 (11.5)	44 (9.6)	
Surgery			
Biopsy/partial	35 (40.2)	188 (41.2)	0.91
Gross/total	52 (59.8)	268 (58.8)	
Histology			
GBM	78 (89.7)	336 (73.7)	0.001
Any MG out of GBM	9 (10.3)	120 (26.3)	
MGMT promoter			
Not methylated	34 (39.1)	152 (33.3)	0.4
Methylated	33 (37.9)	169 (37.1)	
Not available	20 (23.0)	135 (29.6)	
IDH1			
Wild type	40 (46.0)	214 (46.9)	0.041
Mutation	16 (18.4)	42 (9.2)	
Not available	31 (35.6)	200 (43.9)	
Radiotherapy dose			
60 Gy	80 (92.0)	427 (93.6)	0.64
54 Gy	7 (8.0)	29 (6.4)	

GBM glioblastoma, IDH1 isocitrate dehydrogenase 1, KPS Karnofsky Performance Score, MGMT O⁶-methylguanine-DNA methyl-transferase, SD standard deviation

we are confident that our study provides new insights into the management of patients who presented severe myelotoxicity during CRT, an area that has never been investigated before in patients with MG.

Conclusion

We concluded that the majority of patients who received adjuvant TMZ after resolution from myelotoxicity occurred during CRT, where only a fraction of them experienced of toxicity. In addition, the adjuvant CT can positively impact on PFS and OS.

Author contributions Conception and design of study: VV, AP. Acquisition data: AP, AF, GL, RR, PG, SR, LG, CS, EP, GS, GT. Data analysis: LP. Interpretation: AE, VV, AP. Drafting: VV, LP. Revising: AE, AP. Final approval: VV, AP. All authors read and approved submission.

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Data availability The data that support the findings of this study are available on request from the corresponding author, [V.V.]. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Compliance with ethical standards


Conflicts of interest The author declares that they have no conflict of interest.

Consent to participate Informed consent, in line with the principles of the Declaration of Helsinki, was obtained from all individual participants included in the study.

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Authors and Affiliations

Veronica Villani¹  · Elena Anghileri² · Luca Prosperini³ · Giuseppe Lombardi⁴ · Roberta Rudà⁵ · Paola Gaviani⁶ · Simona Rizzato⁷ · Gaetano Lanzetta^{8,11} · Alessandra Fabi⁹ · Claudia Scaringi¹⁰ · Edoardo Pronello⁵ · Giorgia Simonetti⁶ · Giada Targato⁷ · Andrea Pace¹

Elena Anghileri
elena.anghileri@istituto-besta.it

Luca Prosperini
luca.prosperini@gmail.com

Giuseppe Lombardi
giuseppe.lombardi@iov.veneto.it

Roberta Rudà
rudarob@hotmail.com

Paola Gaviani
paola.gaviani@istituto-besta.it

Simona Rizzato
simona.rizzato@asufc.sanita.fvg.it

Gaetano Lanzetta
gaetano.lanzetta@gruppoi.it

Alessandra Fabi
alessandra.fabi@ifo.gov.it

Claudia Scaringi
clascaringi@gmail.com

Edoardo Pronello
pronello.edoardo@gmail.com

Giorgia Simonetti
giorgia.simonetti@istituto-besta.it

Giada Targato
giadatargato@gmail.com

Andrea Pace
andrea.pace@ifo.gov.it

¹ Neuro-Oncology Unit, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi 53, 00144 Rome, Italy

² Molecular Neurooncology Unit Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

³ Department of Neurosciences, S. Camillo-Forlanini Hospital, Rome, Italy

⁴ Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

⁵ Department of Neuro-Oncology, City of Health and Science Hospital, Turin, Italy

⁶ Neuro-Oncology Unit Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

⁷ Department of Oncology, Department of Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy

⁸ Oncology Department, Istituto Neurotraumatologico Italiano, Grottaferrata, RM, Italy

⁹ Phase 1 Unit and Precision Medicine-IRCCS Regina Elena National Cancer Institute, Rome, Italy

¹⁰ Radiation Oncology Unit, UPMC Hillman Cancer Center, San Pietro Hospital FBF, Rome, Italy

¹¹ Scientific Institute for Research, Hospitalization and Health Care (IRCCS) Neuromed, Pozzilli, Italy