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Original Research

Thrombocytopenia limits the feasibility of salvage lomustine chemotherapy in recurrent glioblastoma: a secondary analysis of EORTC 26101

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Abstract ***Background:*** Thrombocytopenia represents the main cause of stopping alkylating chemotherapy for toxicity. Here, we explored the incidence, and the consequences for treatment exposure and survival, of thrombocytopenia induced by lomustine in recurrent glioblastoma. ***Methods:*** We performed a retrospective analysis of the associations of thrombocytopenia with treatment delivery and outcome in EORTC 26101, a randomised trial designed to define the role

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Toxicity;
Transfusion

of lomustine versus bevacizumab versus their combination in recurrent glioblastoma.
Results: A total of 225 patients were treated with lomustine alone (median 1 cycle) (group 1) and 283 patients were treated with lomustine plus bevacizumab (median 3 lomustine cycles) (group 2). Among cycle delays and dose reductions of lomustine for toxicity, thrombocytopenia was the leading cause. Among 129 patients (57%) of group 1 and 187 patients (66%) of group 2 experiencing at least one episode of thrombocytopenia, 36 patients (16%) in group 1 and 93 (33%) in group 2 had their treatment modified because of thrombocytopenia. Lomustine was discontinued for thrombocytopenia in 16 patients (7.1%) in group 1 and in 38 patients (13.4%) in group 2. On adjusted analysis accounting for major prognostic factors, dose modification induced by thrombocytopenia was associated with inferior progression-free survival in patients with *MGMT* promoter-methylated tumours in groups 1 and 2. This effect was noted for overall survival, too, but only for group 2 patients. Conclusion: Drug-induced thrombocytopenia is a major limitation to adequate exposure to lomustine chemotherapy in recurrent glioblastoma. Mitigating thrombocytopenia to enhance lomustine exposure might improve outcome in patients with *MGMT* promoter-methylated tumours.

1. Introduction

The current standard of care treatment for patients with newly diagnosed glioblastoma is surgery as safely feasible followed by radiotherapy with concomitant temozolomide and six cycles of maintenance temozolomide chemotherapy [1]. Recurrence is inevitable, but standards of care for recurrent glioblastoma are less well defined. A minority of patients in the range of 20% may be candidates for second surgery or re-irradiation, but neither of these interventions has been shown to prolong survival in a randomised clinical trial [2]. The majority of patients who are eligible for salvage treatment receive systemic therapy, mostly with lomustine, a nitrosourea compound, or, depending on availability, bevacizumab, an antibody to vascular endothelial growth factor. Lomustine alone has been increasingly considered a standard of care regimen for clinical trials in recurrent glioblastoma [3–5], including the AGILE platform trial [6].

Lomustine, like probably all nitrosoureas, is more active in patients with tumours with promoter methylation of the O^6-methylguanine DNA methyltransferase (*MGMT*) gene [7–9]. However, notably in patients pre-exposed to temozolomide, lomustine chemotherapy carries a high risk of myelosuppression, mostly thrombocytopenia, which may necessitate dose reductions, dose delays, discontinuation of chemotherapy, platelet transfusions and may cause haemorrhages. In the REGAL trial, a phase III randomised study evaluating the efficacy of the vascular endothelial growth factor receptor inhibitor cediranib alone or in combination with lomustine versus lomustine alone [4], Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and 4 thrombocytopenias were observed in 38% and 20%, respectively, in patients treated with cediranib plus lomustine, compared with 22% and 3% in the lomustine alone arm, and 2% and 1% in the cediranib alone arm.

The present secondary analysis of EORTC 26101 [8] sought to explore the extent to which thrombocytopenia interferes with adequate delivery of treatment in patients with recurrent glioblastoma. The rationale for this study was the availability of novel agents like romiplostim that may counteract chemotherapy-induced thrombocytopenia, including glioblastoma [10].

2. Patients and methods

2.1. Patients

To assess the incidence and clinical significance of lomustine-induced thrombocytopenia at first recurrence of glioblastoma, we analysed data from the phase II and III parts of EORTC 26101 (NCT01290939) [8] (Note S1).

2.2. Statistical analysis

We analysed coded individual patient data including date of randomisation, WHO performance status, tumour volume at study entry, steroid use, *MGMT* promoter methylation status, number of treatment cycles, haematological and non-haematological toxicity according to CTCAE v4.0 during study treatment, lomustine dose delays and modifications, lomustine discontinuation, progression-free survival (PFS) and overall survival (Note S2).

SAS version 9.4 (© 2002–2012 per SAS Institute Inc., Cary, NC, USA.) was used for the analyses. For the primary analyses, statistical significance was established at a level of 5%. In descriptive comparison of subgroups,

percentage difference of 10% or more was considered clinically relevant.

3. Results

3.1. Incidence of thrombocytopenia during the study

Analyses were performed on 508 patients: 225 patients treated with lomustine alone (group 1) and 283 patients treated with lomustine plus bevacizumab (group 2) (Fig. S1). Patient characteristics in both groups were similar (Table S1). The median number of lomustine cycles was 1 (range 1–17) in group 1 and 3 (range 1–9) in group 2 [8]. The baseline platelet counts were similar between groups (Table S1). The frequencies with grade of thrombocytopenia per all cycles per patient are detailed in Table S2: 96 patients (43%) in group 1 and 96 patients (34%) in group 2 experienced no single cycle with thrombocytopenia. Conversely, 129 patients (57%) in group 1 and 187 patients (66%) in group 2 experienced at least one cycle with thrombocytopenia. Among the patients who developed at least one episode of thrombocytopenia, at least one more episode was noted in 44 of 129 patients (34%) in group 1 and 107 of 187 patients (57%) in group 2. The likelihood of experiencing no thrombocytopenia remained relatively stable over sequential cycles of lomustine in a range of 50–70% and was similar in both groups (Table S3).

3.2. Impact of thrombocytopenia on lomustine exposure

The overall reasons for lomustine dose delays, dose reductions and discontinuation in both patient groups are shown in Table 1. Lomustine treatment delay, dose reduction and treatment discontinuation due to thrombocytopenia per cycle are shown in Table S4. Progression was the major reason for stopping lomustine, but thrombocytopenia was the major toxicity causing dose delays, dose reductions and discontinuation. Groups did not differ for dose delays and dose-reduced cycles, but relatively more group 1 patients stopped lomustine for

Table 1
Overall causes of lomustine dose delays, dose reductions and discontinuation.

	All lomustine alone cycles (n = 464) Group 1	All lomustine–plus bevacizumab cycles (n = 1071) Group 2
Delayed cycles		
Number of delayed cycles (n, %)		
for any reason	41 (8.8)	111 (10.4)
for toxicity	33 (7.1)	97 (9.1)
for non-haematological toxicity	3 (0.6)	23 (2.1)
for haematological toxicity	30 (6.5)	76 (7.1)
for thrombocytopenia	23 (5.0)	53 (4.9)
for other reasons	8 (1.7)	12 (1.1)
Dose-reduced cycles		
Number of dose-reduced cycles (n, %)		
for any reason	82 (17.7)	143 (13.4)
for toxicity	53 (11.4)	111 (10.4)
for non-haematological toxicity	4 (0.9)	16 (1.5)
for haematological toxicity	50 (10.8)	97 (9.1)
for thrombocytopenia	29 (6.3)	76 (7.1)
for other reasons	29 (6.3)	32 (3.0)
	Lomustine alone patients (n = 225) Group 1	Lomustine plus bevacizumab patients (n = 283) Group 2
Lomustine discontinuation[a]		
for toxicity	25 (11.1)	58 (20.5)
for non-haematological toxicity	4 (1.8)	16 (5.7)
for haematological toxicity	21 (9.3)	42 (14.8)
for thrombocytopenia	16 (7.1)	38 (13.4)[a]
for progressive disease	188 (83.6)	184 (65.0)[a]
for other reasons	12 (5.3)	42 (14.8)
Any reason for lomustine modification		
for toxicity	59 (26.2)	141 (49.8)
for non-haematological toxicity	7 (3.1)	42 (14.8)
for haematological toxicity	54 (24.0)	116 (41.0)
for thrombocytopenia	36 (16.0)	93 (32.9)
for progressive disease	188 (83.6)	184 (65.0)
for other reasons	12 (5.3)	44 (15.5)

[a] One patient discontinued treatment for both thrombocytopenia and progressive disease.

progression whereas more group 2 patients stopped lomustine for toxicity (Table 1).

A total of 42 patients (23%) in group 1 and of 64 patients (26%) in group 2 experienced grade 3 or 4 thrombocytopenia. The frequencies of thrombocytopenia by CTCAE grade, associated delays of the next cycle, dose reductions and discontinuation of lomustine are summarised in Table 2. In group 1, 36 patients experienced treatment modification due to thrombocytopenia, corresponding to 16% (36/225) of

Table 2
Lomustine exposure, thrombocytopenia and haemorrhage.

	Lomustine alone (n = 225) Group 1	Lomustine plus bevacizumab (n = 283) Group 2
Number of lomustine cycles (n, range)		
Median number of lomustine cycles	1 (1–17)	3 (1–9)
Worst grade thrombocytopenia during treatment		
Grade 0	95 (42.2)	94 (33.2)
Grade 1	36 (16.0)	49 (17.3)
Grade 2	41 (18.2)	64 (22.6)
Grade 3	33 (14.7)	59 (20.8)
Grade 4	19 (8.4)	15 (5.3)
Not reported	1 (0.4)	2 (0.7)
Lomustine dose delay		
CTCAE grade 1 thrombocytopenia		
1 delayed cycle (n, %)	4 (1.8)	12 (4.2)
2 delayed cycles (n, %)	0	2 (0.7)
Median duration of delay in days (median,range)	17.5 (14–32)	14.5 (8–28)
CTCAE grade 2 thrombocytopenia		
1 delayed cycle (n, %)	8 (3.6)	17 (6.0)
2 delayed cycles (n, %)	0	1 (0.4)
Median duration of delay in days (median,range)	14.5 (13–19)	14.0 (8–28)
CTCAE grade 3 thrombocytopenia		
1 delayed cycle for grade 3 (n, %)	9 (4.0)	12 (4.2)
2 delayed cycles for grade 3 (n, %)	0	1 (0.4)
Median duration of delay in days (median,range)	14.0 (8–28)	15.0 (8–35)
CTCAE grade 4 thrombocytopenia		
1 delayed cycle (n, %)	2 (0.9)	4 (1.4)
2 delayed cycles (n, %)	0	0
Median duration of delay in days (median, range)	13.5 (13–14)	11 (8–14)
CTCAE any grade thrombocytopenia		
1 delayed cycle (n, %)	23 (10.3)	45 (15.8)
2 delayed cycles (n, %)	0	4 (1.5)
Median duration of delay in days (median,range)	14.0 (8–32)	14.0 (8–35)
Lomustine dose reduction		
for CTCAE grade 1 (not foreseen per protocol) (n, %)	2 (0.9)	11 (3.9)
for CTCAE grade 2 (not foreseen per protocol) (n, %)	6 (2.7)	19 (6.7)
for CTCAE grade 3 (n, %)	16 (7.1)	32 (11.3)
for CTCAE grade 4 (n, %)	4 (1.8)	9 (3.2)
for any CTCAE grade (n,%)	28 (12.4)	71 (25.1)
Lomustine dose discontinuation		
for CTCAE grade 1 (n, %)	2 (0.9)	11 (3.9)
for CTCAE grade 2 (n, %)	4 (1.8)	7 (2.5)
for CTCAE grade 3 (n, %)	4 (1.8)	17 (6.0)
for CTCAE grade 4 (n, %)	6 (2.7)	3 (1.1)
for any CTCAE grade (n, %)	16 (7.1)	38 (13.5)
Platelet transfusion (n, %)		
Patients with at least one platelet transfusion	8 (3.6)	5 (1.7)
Patients with more than one platelet transfusion	6 (2.7)	1 (0.04)
Bleeding		
Intracranial haemorrhage (n, %)		
CTCAE Grade 1	0	3 (1.1)
CTCAE Grade 2	2 (0.9)	2 (0.7)
CTCAE Grade 3	1 (0.4)	0
CTCAE Grade 4	0	0
CTCAE Grade 5	0	1 (0.3)
Any CTCAE grade	3 (1.3)	6 (2.1)
Extracranial haemorrhage	0	0

Abbreviations: n: number of patients, %: percentage.

all patients in group 1 and to 28% (36/129) of patients experiencing at least one episode of thrombocytopenia. In group 2, 93 patients experienced treatment modification due to thrombocytopenia, corresponding to 33% (93/283) of all patients in group 2 and to 50% (93/187) of patients experiencing at least one episode of thrombocytopenia (Table S2, Table S4). Among patients experiencing treatment modification induced by thrombocytopenia, 14 of 36 patients (39%) in group 1 and 27 of 93 patients (29%) in group 2 had their lomustine treatment modified due to thrombocytopenia more than once (Table S5).

3.3. Dose delays

Twenty-three patients (10%) in group 1 and 49 patients (17%) in group 2 had a dose delay for any grade of thrombocytopenia. The median duration of delay was 14 days (Table 2). A similar number of patients with delayed cycles was observed for grade 1/2 versus grade 3/4 thrombocytopenia in group 1 (5% vs. 5%) and group 2 (11% vs. 6%).

3.4. Dose reductions

Twenty-eight patients (12%) in group 1 versus 71 patients (25%) in group 2 had a lomustine dose reduction for any grade of thrombocytopenia (Table 2). As foreseen per protocol, most dose reductions were due to CTCAE grade 3/4 thrombocytopenia: 20 of 28 patients in group 1 and 41 of 71 patients in group 2. Thrombocytopenia was responsible for 29 of 53 cycles (55%) dose-reduced for toxicity in group 1 and 76 of 111 cycles (68%) dose-reduced for toxicity in group 2 (Table 1).

3.5. Discontinuation

Lomustine was discontinued for thrombocytopenia in 16 patients (7%) in group 1 and in 38 patients (13%) in group 2 (Tables 1 and 2), mainly for CTCAE grade 3/4 thrombocytopenia: 10 of 16 patients in group 1 and 20 of 38 patients in group 2. Sixteen of 25 discontinuations for toxicity (64%) in group 1 and 38 of 58 discontinuations for toxicity (66%) in group 2 were due to thrombocytopenia (Table 1).

3.6. Platelet transfusions and haemorrhages

The numbers of documented platelet transfusions (<4%) and haemorrhages were low (<3%). Three patients in group 1 had an intracranial haemorrhage, 2 in the context of grade 2 and 1 in the context of grade 3 thrombocytopenia. Six patients in group 2 had an intracranial haemorrhage, 3 with grade 1, 2 with grade 2 and 1 with grade 5 intracranial haemorrhage. No extracranial haemorrhage was reported in either group (Table 2).

3.7. Association of *MGMT* promoter methylation status with treatment modification induced by lomustine

Table S6 shows that, patients with *MGMT* promoter-methylated glioblastoma experienced more interference with study treatment than patients with *MGMT* promoter-unmethylated tumours. This was expected since these patients remain longer on lomustine owing to the better activity of lomustine in this patient population [8]. Lomustine was discontinued for thrombocytopenia in 2 (3%) versus 7 (11%) patients in group 1, and in 12 (12%) versus 16 (20%) patients in group 2, with tumours without versus with *MGMT* promoter methylation.

3.8. Risk factors for treatment-induced thrombocytopenia

To explore the association between the number of the lomustine cycle or other baseline characteristics and the odds of lomustine treatment modification due to thrombocytopenia, lomustine treatment cycle was dichotomised as first, second and third cycle, versus later cycles. In adjusted analysis, the number of cycles of lomustine treatment was not significantly associated with the odds of lomustine treatment modification for thrombocytopenia, presumably owing to the fact that dose reduction aims at preventing further episodes of thrombocytopenia and does so. Lower baseline platelet counts assessed as a continuous variable ($p < 0.001$), female sex ($p < 0.001$) and WHO performance status above 0 ($p = 0.025$) were associated with higher odds of lomustine treatment modification by thrombocytopenia (Table S7), whereas interval to last prior chemotherapy cycle was not (Note S3).

3.9. Association of treatment modification by thrombocytopenia with PFS

In a risk-adjusted analysis, treatment modification by thrombocytopenia was not significantly associated with PFS. Maximal diameter of the tumour at baseline, steroid use at baseline and *MGMT* promoter methylation status were significantly associated with PFS. PFS was better in patients with smaller (≤40 mm) initial tumour diameter ($p = 0.005$), who did not take steroids at baseline ($p = 0.035$), and who had tumours with *MGMT* promoter methylation ($p < 0.001$) (Table 3). However, a more detailed analysis revealed markable differences by *MGMT* promoter methylation status and treatment (Table 4, Fig. 1): there was an association of treatment modification with superior PFS in patients with MGMT promoter unmethylated tumours, but this effect was largely driven by group 2 patients because only 5 patients in group 1 had a dose modification, owing to the low number of cycles of lomustine in this group. In contrast, patients with MGMT promoter methylated tumours experienced inferior PFS when treatment was modified for thrombocytopenia (Table 4, Note S4).

Table 3
Association between treatment modification by thrombocytopenia and outcome.

Variable	Progression-free survival				Overall survival			
	n = 429, n (%)	HR	95% CI	p-value	n = 505, n (%)	HR	95% CI	p-value
	Unadjusted analysis							
Treatment modification by thrombocytopenia[a]								
No	310 (72.3)	1			381 (75.4)	1		
At least one episode	119 (27.7)	0.99	0.86–1.15	0.942	124 (24.6)	0.82	0.73–0.92	**<0.001**
	Adjusted analysis							
Treatment modification by thrombocytopenia[a]								
No	310 (72.3)	1			381 (75.4)	1		
At least one episode	119 (27.7)	0.90	0.76–1.06	0.223	124 (24.6)	0.77	0.68–0.88	**<0.001**
Age category at baseline								
60 years or below	248 (57.8)	1			291 (57.6)	1		
More than 60 years	181 (42.2)	1.06	0.93–1.22	0.364	214 (42.4)	1.10	0.99–1.21	0.070
Sex								
Male	264 (61.5)	1			312 (61.8)	1		
Female	165 (38.5)	1.00	0.87–1.15	0.995	193 (38.2)	0.98	0.89–1.08	0.679
WHO performance status at baseline								
PS 0	137 (31.9)	1			171 (33.9)	1		
PS 1 or 2	292 (68.1)	1.00	0.86–1.16	0.969	334 (66.1)	0.98	0.88–1.09	0.675
Largest tumour diameter at baseline								
≤40 mm	242 (56.4)	1			275 (54.5)	1		
>40 mm	187 (43.6)	1.25	1.07–1.45	**0.005**	230 (45.5)	1.50	1.34–1.68	**<0.001**
Steroid use at baseline								
No	220 (51.3)	1			254 (50.3)	1		
Yes	209 (48.7)	1.18	1.01–1.37	**0.035**	251 (49.7)	1.69	1.50–1.89	**<0.001**
MGMT promoter								
Unmethylated	136 (31.7)	1			166 (32.9)	1		
Methylated	126 (29.4)	0.40	0.34–0.48	**<0.001**	143 (28.3)	0.60	0.52–0.67	**<0.001**
Undetermined/Not done	167 (38.9)	0.58	0.49–0.69	**<0.001**	196 (38.8)	0.82	0.73–0.92	**<0.001**
Surgery for recurrence								
No	338 (78.8)	1			405 (80.2)	1		
Yes	91 (21.2)	1.01	0.86–1.18	0.940	100 (19.8)	1.09	0.97–1.22	0.145

Abbreviations: MGMT O^6-methylguanine DNA methyltransferase, N number of patients, PS performance status, WHO World Health Organization.
[a] Lomustine treatment modification for thrombocytopenia.

3.10. Association of treatment modification due to thrombocytopenia with OS

Lomustine treatment modification by thrombocytopenia ($p < 0.001$), smaller (≤40 mm) initial tumour diameter ($p < 0.001$), no baseline steroid use ($p < 0.001$) and *MGMT* promoter methylation ($p < 0.001$) were associated with superior OS (Table 3). Again, a more detailed analysis revealed notable differential associations by *MGMT* promoter methylation status and treatment: the association of treatment modification with superior OS in patients with *MGMT* promoter

Table 4
Association of treatment modification by thrombocytopenia with PFS by *MGMT* promoter methylation status and treatment, adjusted for baseline covariates.

Treatment (lomustine) modification by thrombocytopenia	Pooled			*MGMT* promoter unmethylated			*MGMT* promoter methylated		
	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value
	Pooled arms (LOM alone + LOM/BEV)								
	N = 429			N = 136			N = 126		
No	310 (72.3)	1		107 (78.7)	1		79 (62.7)	1	
Yes	119 (27.7)	0.90 (0.76–1.06)	0.223	29 (21.3)	0.39 (0.27–0.57)	***<0.001***	47 (37.3)	1.84 (1.44–2.35)	**<0.001**
	LOM alone arm (group 1)								
	N = 159			N = 43			N = 50		
No	125 (78.6)	1		38 (88.4)	1		33 (66.0)	1	
Yes	34 (21.4)	0.62 (0.46–0.84)	***0.002***	5 (11.6)	0.27 (0.10–0.70)	***0.007***	17 (34.0)	1.73 (1.17–2.57)	***0.006***
	LOM/BEV arm (group 2)								
	N = 270			N = 93			N = 76		
No	185 (68.5)	1		69 (74.2)	1		46 (60.5)	1	
Yes	85 (31.5)	1.09 (0.89–1.33)	0.431	24 (25.8)	0.41 (0.27–0.64)	***<0.001***	30 (39.5)	1.90 (1.34–2.68)	***<0.001***

Abbreviations: MGMT O^6-methylguanine DNA methyltransferase, N number of patients.

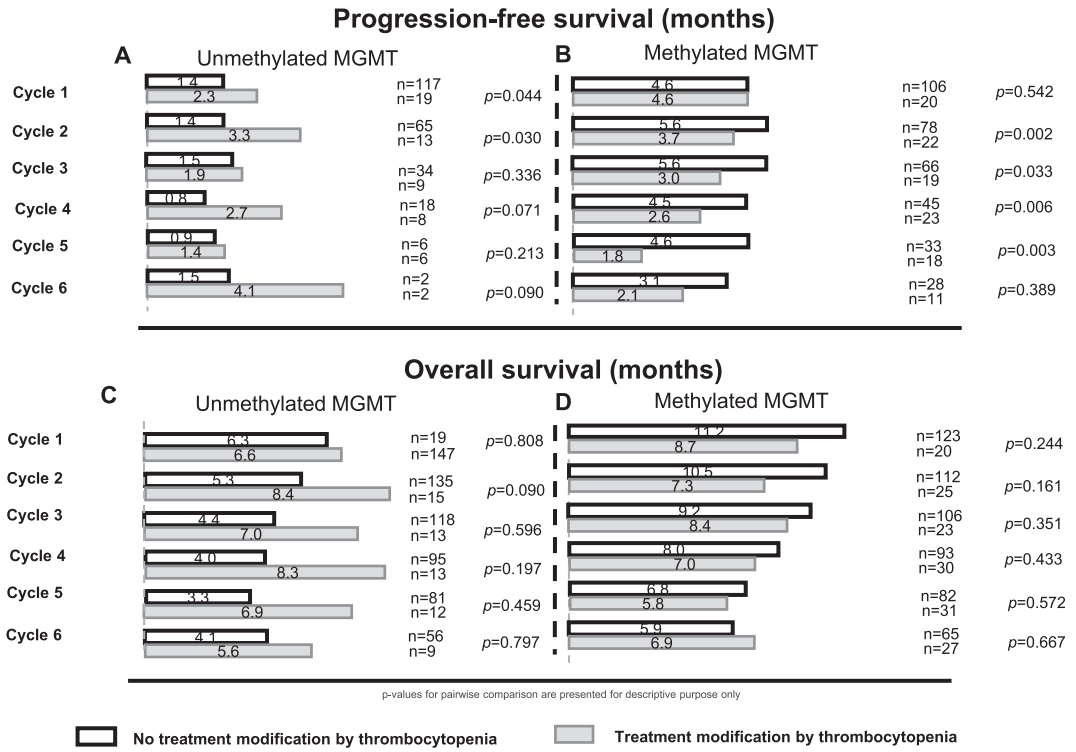

Fig. 1. Progression-free survival and overall survival by MGMT status and treatment modification induced by thrombocytopenia per landmark/cycle. A: PFS in patients with unmethylated MGMT tumour, B: PFS in patients with methylated MGMT tumour, C: OS in patients with unmethylated MGMT tumour, D: OS in patients with methylated MGMT tumour. Landmark analysis performed at each cycle for PFS showed a trend for longer PFS in patients with an MGMT unmethylated glioblastoma when lomustine administration was modified by thrombocytopenia and a longer PFS in patients with a methylated glioblastoma when lomustine could be administered as planned. Landmark analysis performed at each cycle for overall survival showed a trend for longer overall survival in patients with an unmethylated glioblastoma when lomustine administration was modified by thrombocytopenia. The results of the stacked analysis performed pooling the six datasets are presented in Table S8.

unmethylated tumours remained, yet divergent associations became apparent for patients with *MGMT* promoter methylated tumours. The association of inferior OS with treatment modification for thrombocytopenia resembled the observation made for PFS in group 2, but the opposite association was seen for OS in group 1 in that patients with treatment modification had superior OS despite inferior PFS (Table 5, Fig. 1, Note S5).

Table 5
Association of treatment modification by thrombocytopenia with OS by *MGMT* promoter methylation status and treatment, adjusted for baseline covariates.

Treatment (lomustine) modification by thrombocytopenia	Pooled			*MGMT* promoter unmethylated			*MGMT* promoter methylated		
	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value
	Pooled arms (LOM alone + LOM/BEV)								
	N = 505			N = 166			N = 143		
No	381 (75.4)	1		136 (81.9)	1		94 (65.7)	1	
Yes	124 (24.6)	0.77 (0.68–0.88)	***<0.001***	30 (18.1)	0.54 (0.41–0.70)	***<0.001***	49 (34.3)	1.05 (0.82–1.36)	0.697
	LOM alone arm (group 1)								
	N = 223			N = 67			N = 65		
No	188 (84.3)	1		62 (92.5)	1		48 (73.8)	1	
Yes	35 (15.7)	0.69 (0.56–0.85)	***<0.001***	5 (7.5)	0.56 (0.33–0.95)	***0.030***	17 (26.2)	0.55 (0.35–0.85)	***0.008***
	LOM/BEV arm (group 2)								
	N = 282			N = 99			N = 78		
No	193 (68.4)	1		74 (74.7)	1		46 (59.0)	1	
Yes	89 (31.6)	0.80 (0.68–0.95)	***0.009***	25 (25.3)	0.55 (0.40–0.76)	***<0.001***	32 (41.0)	1.71 (1.27–2.31)	***<0.001***

Abbreviations: MGMT O^6-methylguanine DNA methyltransferase, N number of patients.

4. Discussion

Chemotherapies used for the treatment of primary brain tumours frequently induce myelotoxicity, and thrombocytopenia represents the main cause of stopping alkylating agent chemotherapy for toxicity [1,11,12]. Consequences of thrombocytopenia include postponed chemotherapy courses, dose reductions, discontinuation of chemotherapy, as well as haemorrhages, including cerebral intratumoural bleeding, with increased risk in patients treated with corticosteroids [13,14]. Until recently, platelet transfusions were the only treatment option for severe chemotherapy-induced thrombocytopenia. The efficacy of a new thrombopoietin mimetic agent romiplostim (AMG 531, Nplate®, Amgen), to counteract chemotherapy-induced thrombocytopenia, has been shown in a phase II open label multicenter single arm phase II trial (NCT 02227576) in newly diagnosed glioblastoma [10].

Here, we used the clinical trial database of the EORTC trial 26101 [8] to estimate the impact of thrombocytopenia on lomustine exposure and outcome of patients with recurrent glioblastoma treated with lomustine alone or in combination with bevacizumab (Note S6).

The apparent association between drug-induced thrombocytopenia and improved outcome in patients with tumours lacking *MGMT* promoter methylation, mainly driven by patients in group 2, remains incompletely understood. Of note, lomustine is considered essentially inactive in this group of tumours [9]. Moreover, the overall short exposure to lomustine (Table S6) may render this analysis sensitive to chance findings (Figs. S3 and S4). The alternative explanation that lomustine may be detrimental in this group of patients requires further study although the outcome data of the BELOB trial that allow to compare bevacizumab alone with the combination of bevacizumab and lomustine do not support this notion [7]. Importantly, the positive association of treatment modification with outcome was largely driven by group 2 patients (Tables 4 and 5).

The occurrence of dose delay, dose reduction or treatment interruption was associated with inferior PFS in patients with *MGMT* promoter-methylated tumours. The association of lomustine modification induced by thrombocytopenia with inferior PFS in patients with *MGMT* promoter-methylated tumours appears to confirm the hypothesis that thrombocytopenia prevents adequate lomustine exposure. Although group 1 patients started with a higher dose of lomustine than group 2 patients, there was no difference in overall survival, potentially confounded by the cotreatment with bevacizumab in group 2 [8]. That patients with *MGMT* promoter-methylated tumours in group 1 who had treatment modification for thrombocytopenia experienced inferior PFS, but still better OS is a puzzling observation that revives the idea that myelosuppression may predict overall outcome [15,16], a hypothesis that we did not confirm at least in the newly diagnosed setting [17]. Furthermore, temozolomide dose intensification in the newly diagnosed setting did not improve outcome [18]. Overall, our study may lend support to the hypothesis that individualised dosing may be superior to flat dosing based on body surface area and indicates that individual dose escalation schemes may make sense. We also provide a clear-cut post hoc rationale for the RIGOLETTO EORTC 1926 trial (NCT04933942) that explores romiplostim salvage in the setting of lomustine-induced thrombocytopenia.

Since bevacizumab is still used in combination with lomustine in various countries and centres, based on the clear superiority for PFS in the 26101 trial over lomustine alone, we included an analysis of this combination with some important observations. Lomustine was discontinued for thrombocytopenia more often with the combination, which may confirm that bevacizumab contributes to thrombocytopenia although patients also merely received more lomustine in this cohort (Table S6). It may also reflect the assumption that, at least in patients with tumours lacking MGMT promoter methylation, lomustine is perceived as not contributing to the treatment effect.

Our study has limitations. Although the data were assembled prospectively, the present analysis is a post hoc analysis, and items such as platelet transfusions and haemorrhages may have been underreported. Confounding effects of comedications could not be modelled. Data on number of cycles of temozolomide prior to treatment with lomustine were not available to explore a potential role as a risk factor. Further, the observations regarding the comparison of groups 1 and 2 need to be interpreted with caution. Group 1 started with a higher dose of lomustine, but longer PFS mediated by bevacizumab allowed patients in group 2 to receive a median of 3 rather than 1 lomustine cycles as in the control arm [8]. We cannot distinguish whether thrombocytopenia *per se* or the introduction of changes to the treatment regimen were prognostic in our adjusted analyses.

More individualised treatment regimens may have to be explored in a disease setting where standards of care have not been improved over decades. These findings encourage the evaluation of therapeutic approaches allowing to maintain the recommended doses of lomustine in patients with recurrent glioblastoma with *MGMT* promoter methylation, as previously proposed for allowing adequate temozolomide exposure in the newly diagnosed setting [10].

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Author contributions

Experimental design and its implementation: ELR, FBO, TG, MW.

Acquisition, analysis, or interpretation of data: all authors.

Statistical analysis: FBO, TG.

Writing of the manuscript: all authors.

Conflict of interest statement

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Appendix A. Supplementary data

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