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How did lomustine become standard of care in recurrent glioblastoma?

Michael Weller[a,*], Emilie Le Rhun[a,b,c,d]

[a] Department of Neurology, Brain Tumor Center & Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland
[b] University of Lille, Inserm, U-1192, F-59000 Lille, France
[c] CHU Lille, Neuro-Oncology, General and Stereotaxic Neurosurgery Service, F-59000 Lille, France
[d] Oscar Lambret Center, Neurology, F-59000 Lille, France

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ABSTRACT

Glioblastomas are the most common malignant primary intrinsic brain tumors. Their incidence increases with age, and males are more often affected. First-line management includes maximum safe surgical resection followed by involved-field radiotherapy plus concomitant and six cycles of maintenance temozolomide chemotherapy. Standards of care at recurrence are much less well defined. Minorities of patients are offered second surgery or re-irradiation, but data on a positive impact on survival from randomized trials are lacking. The majority of patients who are eligible for salvage therapy receive systemic treatment, mostly with nitrosourea-based regimens or, depending on availability, bevacizumab alone or in various combinations. In clinical trials, lomustine alone has been increasingly used as a control arm, assigning this drug a standard-of-care position in the setting of recurrent glioblastoma. Here we review the activity of lomustine in the treatment of diffuse gliomas of adulthood in various settings. The most compelling data for lomustine stem from three randomized trials when lomustine was combined with procarbazine and vincristine as the PCV regimen in the newly diagnosed setting together with radiotherapy; improved survival with PCV was restricted to patients with isocitrate dehydrogenase-mutant tumors. No other agent with the possible exception of regorafenib has shown superior activity to lomustine in recurrent glioblastoma, but activity is largely restricted to patients with tumors with O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation. Hematological toxicity, notably thrombocytopenia often limits adequate exposure.

Introduction

Lomustine, also known as CCNU (chloroethyl-cyclohexyl-nitrosourea), is an alkylating agent of the nitrosourea family [1–3] (Fig. 1). It is a monofunctional alkylating agent which alkylates DNA and RNA and can cross-link DNA and thus acts in a cell cycle-dependent and -independent manner. One of the most relevant lesions induced by lomustine, the formation of O^6-chloroethylguanine, can be reverted by O^6-methylguanine DNA methyltransferase (MGMT). Lomustine may also inhibit enzymatic functions by carbamoylation of amino acids but the contribution of this activity to clinical activity remains unknown. As a lipid-soluble drug, it permeates the blood brain barrier well which *a priori* made it a reasonable candidate for the chemotherapy of intrinsic brain tumors. It is administered orally in six to eight weeks intervals, given its delayed myelosuppressive properties with nadirs at 5 weeks after administration.

Lomustine in recurrent glioblastoma

Table 1 summarizes data from all published randomized clinical trials in recurrent glioblastoma that used lomustine as a control arm [4–11]. These trials revealed a low objective response rate to lomustine in the range of 10% and a median progression-free survival that does not exceed 2 months. Progression-free survival at 6 months, a common endpoint in such trials, was in the range of 20% which today is considered a benchmark for planning randomized trials in this setting. The few trials that reported outcome by MGMT promoter methylation status [6,8,10] revealed low activity, if at all, in patients with tumors lacking MGMT promoter methylation.

Overall survival from randomization in all trials was in the range of 6–9 months and differences in overall survival between trials are probably largely driven by patient selection. None of the experimental agents was superior to lomustine with the possible exception of regorafenib, however, the REGOMA trial was a medium-sized phase II trial and several prognostic factor imbalances favored the regorafenib group:

* Corresponding author at: Department of Neurology, University Hospital and University of Zurich, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland.
E-mail address: michael.weller@usz.ch (M. Weller).

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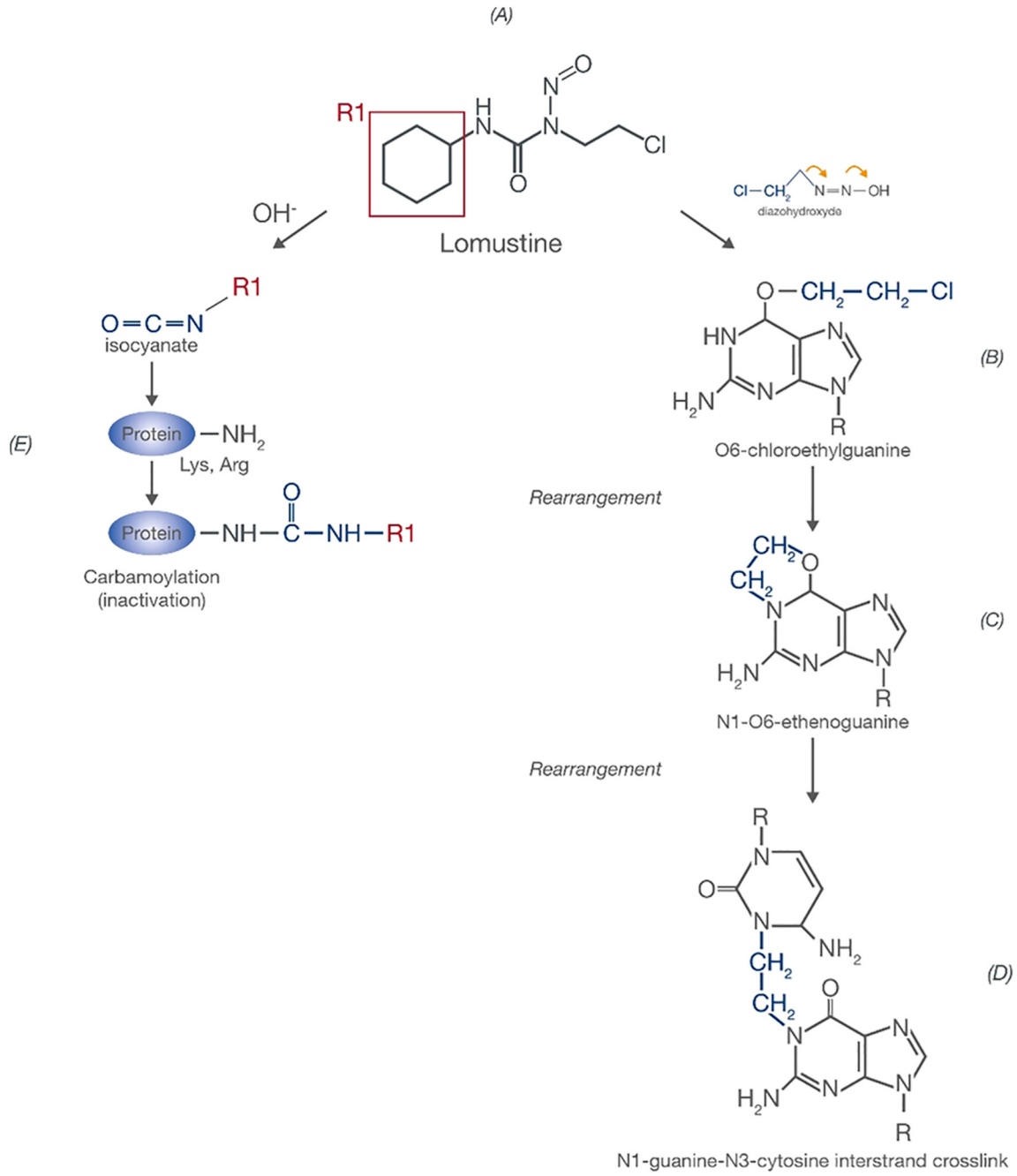

Fig. 1. Chemical structure and major mode of action of the nitrosourea lomustine (adapted from [2,3]). A. Chemical structure of lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea). B-D. Mechanism of DNA crosslinking. Chlorethylation of guanine at the O^6 site generates O^6-chloroethylguanine by the active metabolite diazohydroxide (B). Intramolecular rearrangement of O^6-chloroethylguanine to N^1-O^6-ethenoguanine (C). Formation of a N^1-guanine-N^3-cytosine interstrand crosslink (D). Carbamoylation of lysine or arginine residues and thus inactivation of proteins via the active metabolite isocyanate (E).

patients were on steroids less frequently, were younger, had more often MGMT promoter-methylated tumors, and had a longer progression-free survival with first-line therapy. Furthermore, cross-trial comparison indicates particularly poor outcome with lomustine in the REGOMA trial [10]. While this observation is held as an argument against the validity of the data from the REGOMA trial, it is still a randomized clinical trial, and enrollment of a poor prognosis patient population is probably a better explanation for this poorer outcome.

Quite obviously, the one trial that is missing is a simple comparison of lomustine with placebo or best standard of care to demonstrate that lomustine has indeed activity in recurrent glioblastoma. In that regard, a small Belgian trial on axitinib comes closest to such a design because the combination of lomustine with axitinib was compared with axitinib alone [9]. Somewhat unexpectedly, this trial indicated no additional activity of lomustine in this setting of combination with axitinib. One may speculate whether this even reflects partially antagonistic activity of axitinib and lomustine, either on a biochemical level or at the level of lomustine penetration to the tumor tissue. Anyhow, this trial has received very little attention, probably because of small sample size, because of the mixing of axitinib-treated patients from various stages of the trial, and because of a mixed population of patients with first and later recurrences of glioblastoma.

Table 1
Clinical trials of CCNU in recurrent glioblastoma.

Trial/reference	Response rate	Progression-free survival (PFS) (months)	HR	PFS at 6 months (%)	HR	Overall survival (OS) (months)	HR
STEERING							
Wick et al. 2010 [4]							
Randomized phase III, open label							
Enzastaurin (266)	5 responses	1.5	1.28 (0.97–1.70)	11		6.6	1.20 (0.88–1.65)
Lomustine (92)	4 responses	1.6		19		7.1	
REGAL							
Batchelor et al. 2013 [5]							
Randomized phase III, partially blinded							
Cediranib (131)	1 CR, 17 PR	3.1 (2.7–4.3)	1.05 (0.74–1.50), p = 0.90	16		8	1.43 (0.96–2.13), p = 0.10
Cediranib plus lomustine (1 2 9)	2CR, 19 PR	4.2 (2.8–6.7)	0.76 (0.53–1.08), p = 0.16	35		9.4	1.15 (0.77–1.72), p = 0.50
Lomustine (65)	5 PR	2.7 (1.4–5.6)		25		9.8	
BELOB							
Taal et al. 2014 [6]							
Randomized phase II, open label	ORR						
Bevacizumab (50)	38 (24–53)	3 (3–4)		16 (7–27)		8 (6–9)	
Bevacizumab plus lomustine (90 mg/m^2) (44)	34 (20–51)	4 (3–8)		41 (26–55)		11 (8–12)	
Lomustine (46)	5 (1–17)	1 (1–3)		13 (5–24)		8 (6–11)	
Bevacizumab							
MGMT unmethylated (24)				8 (1–23)	1		
MGMT methylated (18)				33 (14–55)	0.43 (0.21–0.85)		
Bevacizumab plus lomustine (90/110 mg/m^2)							
MGMT unmethylated (26)				23 (9–40)			
MGMT methylated (11)				62 (38–79)	0.41 (0.22–0.77)		
Lomustine							
MGMT unmethylated (20)				0	1		
MGMT methylated (23)				26 (11–45)	0.56 (0.37–0.77)		
Brandes et al. 2016 [7]							
Randomized phase II, partially blinded							
Galunisertib (40))	2 PR	1.8 (1.6–3.0)		15 (5–28)		8.0 (5.7–11.7)	0.93 (0.58–1.49)
Galunisertib plus lomustine (79)	1 CR	1.8 (1.7–1.8)		6 (2–13)		6.7 (5.3–8.5)	1.13 (0.78–1.65)
Lomustine plus placebo (39)	None	1.9 (1.7–1.9)		6 (1–18)		7.5 (5.6–10.3)	
Wick et al. 2017 [8]							
Randomized phase III, open label							
Bevacizumab plus lomustine (288)	5 CR, 103 PR	4.2 (3.7–4.3)	0.49 (0.39–0.61), p < 0.001			9.1 (8.1–10.1)	0.95 (0.74–1.21), p = 0.65
Lomustine (149)	1 CR, 18 PR	1.5 (1.5–2.5)				8.6 (7.6–10.4)	
Bevacizumab plus lomustine							
MGMT unmethylated (102)		3.0 (2.8–3.7)		12.7 (7.1–19.9)		8.0 (6.9–9.1)	
MGMT methylated (78)		6.9 (5.6–8.3)		58.4 (46.9–68.7)		12.6 (10.6–16.1)	
Lomustine							
MGMT unmethylated (44)		1.5 (1.4–1.5)		2.3 (0.2–10.4)		7.2 (4.8–8.6)	
MGMT methylated (46)		3.0 (1.6–5.1)		30.4 (18.0–43.9)		10.4 (8.3–13.5)	
Duerinck et al. 2018 [9]							
Randomized phase II, open label, glioblastoma at first or later relapses							
Axitinib (50)	3 CR, 11 PR	2.9 (2.6–2.8)		26 (13–38)		12.4 (4.7–16.3)	
Axitinib plus lomustine (29)	11 PR	3 (1.4–4.7)		24 (8–39)		11.7 (7.9–15.6)	
REGOMA							
Lombardi et al. 2018 [10]							
Randomized phase II, open label							
Regorafenib (59)	1 CR, 2 PR	2 (1.9–3.6)	0.65 (0.45–0.95)	16.9 (8.7–27.5)		7.4 (5.8–12.0)	0.50 (0.33–0.75). p = 0.0009
Lomustine (60)	1 CR, 1 PR	1.9 (1.8–2.1)		8.3 (3.1–17.0)		5.6 (4.7–7.3)	
Regorafenib							
MGMT unmethylated (30)							0.43 (0.23–0.80) p = 0.028
MGMT methylated (29)							0.57 (0.33–0.97) p = 0.015

(*continued on next page*)

Table 1 (*continued*)

Trial/reference	Response rate	Progression-free survival (PFS) (months)	HR	PFS at 6 months (%)	HR	Overall survival (OS) (months)	HR
Lomustine							
MGMT unmethylated (32)							
MGMT methylated (27)							
van den Bent et al. 2019 [11]							
Randomized phase II, open label, EGFR-amplified glioblastoma							
ABT-414 (86)	2 PR	1.9				7.9	1.04 (0.73–1.49, p = 0.83
ABT-414 plus temozolomide (88)	5 PR	2.7				9.6	0.71 (0.50–1.02), p = 0.62
Lomustine or temozolomide (86)	1 PR	1.9				8.2	

Abbreviations: ND no data, OS overall survival, PFS progression-free survival, TMZ temozolomide.

Lomustine in newly diagnosed glioblastoma?

No contemporary trial has explored whether the addition of lomustine to standard of care radiotherapy would improve outcome in subsets of gliomas of adulthood. One might speculate that similar results as obtained with temozolomide in glioblastoma should also possibly be achieved with a nitrosourea compound. Yet, the disappointing results with lomustine as part of the PCV regimen in a historical United Kingdom trial do not support this expectation (see below) [12]. Conversely, the CeTeG trial renewed interest in lomustine as part of the management in the first-line setting (see below) [13].

Lomustine as part of the PCV regimen

Undoubtedly the most convincing efficacy data for lomustine have been generated when the drug was used in combination with another alkylating agent, procarbazine, and the antimitotic agent, vincristine, as the PCV protocol. This protocol was first used in unselected brain tumor patients in 1975, based on single agent and preclinical data, and was not felt to be superior to carmustine at the time [14]. The most commonly used version of PCV today includes lomustine given at 110 mg/m^2 p.o. on day 1, procarbazine given at 60 mg/m^2 p.o. on days 8–21, and vincristine given at 1.4 mg/m^2 at days 8 and 29 of a six-to-eight week cycle. Of note, two negative clinical trials conducted in the United Kingdom used a different regimen that uses lomustine at 100 mg/m^2 p.o. on day 1, procarbazine at 100 mg/m^2 p.o. on days 1–10, and vincristine at 1.5 mg/m^2 on day 1 of a six week cycle [12,15]. Vincristine is commonly capped at a total dose of 2 mg.

The PCV regimen has demonstrated superiority when combined with radiotherapy over radiotherapy alone in three randomized clinical trials of lower (II/III) WHO grade gliomas (Table 2) [12,15–18]. Subgroup analyses from these trials allowed to conclude that PCV is most active in 1p19q-codeleted tumors (oligodendrogliomas) followed by isocitrate dehydrogenase (*IDH*) mutant astrocytomas whereas activity in *IDH* wild-type tumors remains uncertain. This is because the latter tumors were underrepresented in the three clinical trials and because prior studies of PCV in the newly diagnosed or recurrent setting of mostly *IDH* wild-type (presumably) gliomas in the United Kingdom had not demonstrated superiority when PCV was combined with radiotherapy over radiotherapy alone in the newly diagnosed setting, or over temozolomide alone in the recurrent setting (Table 2). It has remained an area of controversy to date to what extent procarbazine and vincristine contribute to the efficacy of the PCV regimen.

Vincristine does not cross the blood brain barrier, accordingly, it has been repeatedly proposed to omit this drug from the PCV regimen, assuming that it cannot reach its target, and also because of significant toxicity in terms of peripheral neuropathy upon prolonged use. No clinical trial has compared PCV with a PC regimen, that has e.g., been used in large tumors then referred to as gliomatosis cerebri [19] and the patient numbers required to demonstrate that vincristine can be safely omitted would probably be enormous. Yet, two retrospective case series have not reported inferior outcome with a PC regimen as opposed to PCV in oligodendroglial tumors [20,21].

Procarbazine is another alkylating agent chemically related to temozolomide that has inferior activity in recurrent glioblastoma as a single agent compared with temozolomide [22]. Accordingly, there was a rationale to improve PCV by replacing procarbazine by temozolomide and by omitting vincristine to design a novel alkylator combination for newly diagnosed glioblastoma [23,24]. UKT-03 was a small phase II trial that was in part designed to overcome MGMT-mediated chemoresistance, assuming that exposure to temozolomide for five days directly after lomustine intake might deplete MGMT and thus improve the efficacy of lomustine. However, compared with historical controls, this small trial appeared to indicate no benefit in MGMT promoter unmethylated glioblastoma, but rather a strong survival signal in patients with MGMT promoter methylated glioblastoma. Accordingly, this combination was taken forward to a randomized phase III trial, CeTeG, in this subset of patients. While patient numbers were small and while there were imbalances of prognostic factors of patients at three sites, there was still overall a signal of prolonged survival for the temozolomide-lomustine combination over standard of care [13]. The idea of combing temozolomide with lomustine has also been adopted for pediatric malignant gliomas) [25,26].

The efficacy signal with combining temozolomide and lomustine in the CeTeG trial [13] suggests that there may be true synergistic activities of different alkylating agents that warrant further study [3,27]. This is because simply doubling the dose of temozolomide in the newly diagnosed setting, as explored in the RTOG 0525 trial, had no effect at all on progression-free or overall survival [28].

Tolerability and safety of lomustine

Lomustine is an emetogenic chemotherapeutic agent that requires standard antiemetic agent prophylaxis which is commonly sufficiently active. The clinically most relevant toxicities documented in clinical trials are summarized in Table 3 [4–11]. Thrombocytopenia emerges as the most important toxicity overall and often requires dose reductions, delays of cycles or even discontinuation of treatment. Neutropenia and lymphocytopenia are comparably less frequent and less severe. Despite this toxicity profile, myelodysplastic syndromes and leukemia are rare as sequelae of lomustine chemotherapy presumably because the limited life expectancy of glioma patients reduces the risk of complications that may occur years after exposure [29], yet, given the increasing use of the PCV regimen in patients with lower WHO grade tumors with a median survival of 15–20 years, the incidence of such delayed haematological complications may increase.

Table 2
Randomized clinical trials of PCV polychemotherapy in patients with diffuse gliomas of WHO grades II-IV.

		Progression-free survival (PFS) [years]				Overall survival (OS) [years]		
BR05								
MRC Brain Tumor Working Party 2001 [12]								
Randomized, open label, phase III, newly diagnosed WHO grade III/IV astrocytoma	RT (339)	RT → PCV (335)			RT (339)	RT → PCV (335)	HR (95% CI)	P
	No data	No data			9.5	10.0	0.95 (0.81–1.11)	0.50
Brada et al. 2010 [15]								
Randomized, open label, phase III, recurrent high-grade glioma	PCV (224)	TMZ 5/23 (112) or TMZ 21/7 (111)	HR (95% CI)	P	PCV (224)	TMZ 5/23 (112) or TMZ 21/7 (111)	HR (95% CI)	P
	3.6	4.7	0.89 (0.73–1.08)	0.23	6.7	7.2	0.91 (0.74–1.11)	0.35
RTOG 9402								
Cairncross et al. 2013 [16]								
Randomized, open label, phase III, newly diagnosed anaplastic oligodendroglioma or oligoastrocytoma	RT (14 3)	PCV → RT (148)	HR (95% CI)	P	RT (143)	PCV → RT (148)	HR (95% CI)	P
All patients (291)	No update in 2013	No update in 2013			4.7	4.6	0.79 (0.6–1.4)	
1p/19q-codeleted (126)	2.9	8.4	0.47 (0.3–0.72)		7.3	14.7	0.59 (0.37–0.95)	
1p/19q-non-codeleted (137)	1	1.2	0.81 (0.56–1.16)		2.7	2.6	0.85 (0.58–1.23)	
EORTC 26951								
Van den Bent et al. 2013 [17]								
Randomized, open label, phase III, newly diagnosed anaplastic oligodendroglioma or oligoastrocytoma	RT (183)	RT → PCV (185)	HR (95% CI)		RT (183)	RT → PCV (185)	HR (95% CI)	
All patients (368)	1.1	2.0	0.66 (0.52–0.83)		2.5	3.5	0.75 (0.6–0.95)	
1p/19q-codeleted (80)	4.2	13.1	0.42 (0.24–0.74)		9.3	Not reached	0.56 (0.31–1.03)	
1p/19q-non-codeleted (236)	0.7	1.2	0.73 (0.56–0.97)		1.8	2.1	0.83 (0.62–1.1)	
RTOG 9802								
Buckner et al. 2016 [18]								
Randomized, open label, phase III, WHO grade II oligodendroglioma, oligoastrocytoma, astrocytoma	RT (126)	RT → PCV (125)	HR (95% CI)	P	RT (126)	RT → PCV (125)	HR (95% CI)	P
All patients (251)	4 (3.1–5.5)	10.4 (6.1-not reached)	0.50 (0.36–0.68)	< 0.001	7.8	13.3	0.59 (0.42–0.83)	0.03
Patients with $IDH1^{R132H}$-mutant tumors (71)			0.32 (0.17–0.62)	< 0.001			0.42 (0.20–0.86)	0.02

Table 3
Toxicity of lomustine in clinical trials in recurrent glioblastoma.

Trial/reference	Hematological toxicity						Non-hematological toxicity				
	Thrombocytopenia Grades 1–2	Thrombocytopenia Grades 3–4	Neutropenia Grades 1–2	Neutropenia Grades 3–4	Lymphopenia Grades 1–2	Lymphopenia Grades 3–4	Liver enzymes Grades 1–2	Liver enzymes Grades 3–4	Respiratory toxicity Grades 1–2	Respiratory toxicity Grades 3–4	Comments
STEERING											
Wick et al. 2010 [4]											
	Grade 2 only		Grade 2 only		Grade 2 only						
Enzastaurin (167)	4 (2)	1 (1)	1 (1)	0	0	0					
Lomustine (84)	9 (11)	21 (25)	4 (5)	17 (20)	2 (2)	0					
REGAL											
Batchelor et al. 2013 [5]											
Cediranib (128)		2 (2)		1 (1)		3 (2)		4 (3)		4 (3) PE	
Cediranib plus lomustine (123)		47 (38)		25 (20)		5 (4)		14 (11)		6 (5) PE	
Lomustine (64)		14 (22)		2 (3)		5 (8)		0		4 (6) PE	
BELOB											
Taal et al. 2014 [6]											
Randomized phase II, open label			Only while blood cell count available								
Bevacizumab (50)	49 (98)	1 (2)	50 (100)	0					5 (10)	2 (4)	
Bevacizumab plus lomustine (9o mg/m^2) (44)	40 (91)	4 (9)	41 (93)	3 (7)					15 (34)	0	
Lomustine (44)	37 (81)	9 (19)	38 (82)	8 (17%)					1 (2)	0	
Brandes et al. 2016 [7]											
Randomized phase II, partially blinded											
Galunisertib (40)	2 (5)	0	2 (0)	0	0	1 (3)					
Galunisertib plus lomustine (78)	16 (21)	6 (8)	4 (5)	6 (8)	2 (3)	7 (9)					
Lomustine (39)	10 (26)	5 (13)	4 (10)	2 (5)	2 (5)	0					
Duerinck et al. 2018 [9]											
Randomized phase II, open label, glioblastoma at first or later relapses											
Axitinib	0	3 (6)		0		3 (6)					
Axitinib plus lomustine	10 (34)	9 (31)		6 (21)		3 (10)					
REGOMA											
Lombardi et al. 2018 [10]											
Randomized phase II, open label											
Regorafenib (59)	12 (20)	1 (2)	1 (2)	1 (2)	2 (3)	3 (5)	6 (10)	2 (4)			
Lomustine (60)	18 (30)	8 (13)	4 (7)	7 (12)	2 (3)	8 (13)	1 (2)	2 (3)			
van den Bent et al. 2019 [11]											
Randomized phase II, open label, EGFR-amplified glioblastoma											
ABT-414 (84)	0	1 (1)	5 (6)	0	0	10 (12)	33 (39)	0	6 (7)	0	
ABT-414 plus temozolomide (88)	54 (61)	7 (8)	14 (16)	3 (3)	35 (40)	26 (30)	49 (56)	0	15 (17)	5 (6) (2 PE)	
Lomustine (56)	36 (64)	14 (25)	14 (25)	10 (18)	25 (45)	18 (32)	19 (34)	2 (4)	9 (16)	3 (5) (all PE)	Unclear whether seen with lomustine or temozolomide

Abbreviations: ND no data, OS overall survival, PFS progression-free survival, TMZ temozolomide.

Non-haematological toxicities are of less concern, although liver toxicity remains an issue notably in combination with other potentially hepatotoxic drugs. Pulmonary fibrosis, a potentially life threatening toxicity associated with nitrosourea treatment, has not been documented to be a toxicity of concern in clinical trials where toxicity was carefully documented. The absence of relevant rates of severe pulmonary toxicity does not justify to monitor lung function in otherwise asymptomatic patients when planning clinical trials with lomustine.

Conclusions

Lomustine probably remains the most widely used drug second only to temozolomide in the treatment of gliomas. Despite all limitations summarized above, it is defined as the main standard of care for recurrent glioblastoma in Europe, where bevacizumab is not approved, in the EANO guideline [30], and also in the *Adaptive Global Innovative Learning Environment for Glioblastoma* (AGILE) consortium [31]. Moreover, lomustine is likely the key component of the PCV regimen which has become standard of care in most lower WHO grade gliomas with IDH mutation.

There is little doubt that exposure to lomustine could be improved in patients with lomustine-sensitive tumors like oligodendrogliomas or *MGMT* promoter-methylated glioblastoma if the key toxicities where mitigated. One such avenue would be the administration of drugs like romiplostim, a thrombopoietin receptor agonist recently shown to allow adequate exposure to temozolomide in patients with newly diagnosed glioblastoma experiencing severe thrombocytopenia [32]. For clinical trials in recurrent glioblastoma, while lomustine remains the standard of care, differential sample size calculations and outcome expectations based on the rate of patients with MGMT promoter-methylated tumors enrolled into the trial should be considered.

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