CLINICAL STUDY

Multicenter, single arm, phase II trial on the efficacy of ortataxel in recurrent glioblastoma

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Abstract

Background and purpose Glioblastoma (GBM) is the most aggressive and frequent subtype of all malignant gliomas. At the time of recurrence, therapeutic options are lacking. Ortataxel, a second-generation taxane was reported to be effective in pre-clinical and phase I clinical studies. The aim of this study was to evaluate a potential therapeutic activity of ortataxel in patients with GBM recurring after surgery and first line treatment.

Methods In this phase II study, according to a two stage design, adult patients with histologically confirmed GBM in recurrence after surgery or biopsy, standard radiotherapy and chemotherapy with temozolomide were considered eligible. Patients included were treated with ortataxel 75 mg/m^2 i.v. every 3 weeks until disease progression. The primary objective of the study was to evaluate the activity of ortataxel in terms of progression free survival (PFS) at 6 months after the enrollment. PFS, overall survival at 9 months after the enrollment, objective response rate, compliance and safety were evaluated as secondary endpoints.

Results Between Nov 26, 2013 and Dec 12, 2015, 40 patients were recruited across six centres. The number of patients alive and free from progression at 6 months after the enrollment, observed in the first stage was four (11.4%), out of 35 patients included in the analysis, below the minimum number of events (7 out of 33) required to continue the study with the second stage The most important toxicities were neutropenia and hepatotoxicity that occurred in 13.2% of patients and leukopenia that occurred in 15.8% of patients.

Conclusion Overall ortataxel treatment fail to demonstrate a significant activity in recurrent GBM patients. However in a limited number of patients the drug produced a benefit that lasted for a long time.

Trial registration: This study is registered with ClinicalTrials.gov, number NCT01989884.

Keywords Glioblastoma · Ortataxel · Recurrence · Taxane

Introduction

The incidence of primary CNS tumors in Europe is about 5/100,000 cases per year and malignant gliomas account for about 90% [1]. Among all malignant gliomas, glioblastoma

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(GBM) accounts for 60–70% and it remains the most aggressive subtype as well as the most frequently diagnosed in adults, with a median age onset of 64 years. With 1- and 5-year overall survival (OS) rates of 29% and 3%, respectively, the prognosis of GBM remains poor [2]. Even with current standard of care [3] for newly diagnosed GBM, the majority of GBMs recur within a year. At the time of recurrence, therapeutic options are lacking and the development of more effective therapeutic approaches is imperative. The available salvage therapies are modestly effective, and no single treatment can be considered the standard of care. Available options include: repeat surgery, stereotactic radiosurgery, combinations of repeat surgery with local/second line chemotherapy [4], re-challenge with metronomic temozolomide [5, 6], anti-angiogenic treatment with bevacizumab [7], and fotemustine [8], with the proportion of disease-free patients at 6 months (PFS-6) is 15%. None of therapeutic options explored are supported by class I evidence obtained in a randomized, controlled, phase III trials, except for repeat surgery followed by locoregional nitrosourea (Gliadel), which was shown to be superior to repeat surgery alone by Brem and colleagues [9]. Among all mentioned options, fotemustine, a third generation nitrosourea, is one of the most practiced in the setting of GBM relapse. Fotemustine has shown a response rate up to 70% in sporadic retrospective series of patients with recurrent malignant gliomas [10]. More recent studies suggest interesting PFS-6 ranging from 20.9 to 48% with most reports around 20% [11] up to 26.7% [12] although in association with procarbazine.

Although taxanes such as paclitaxel and docetaxel are active in vitro against glioblastoma cell lines (U-87 MG and U-118 MG) they are not potentially effective drugs in vivo as they do not cross the blood–brain barrier (BBB) [13, 14]. Some molecules, analogs to first generation taxanes (named taxane of second generation) showed, in preclinical models, the ability to cross the BBB, and have been tested for antitumor activity also in human glioblastoma xenografts in comparison with paclitaxel and docetaxel. Speculatively, the penetration of these second-generation taxanes in the central nervous system (CNS) is related to the fact that they are a poor substrate of P-gp170, which are known to play an inhibitory role in the BBB passage of xenobiotica in the CNS.

Cabazitaxel is one of these analogs that was tested in different animal species bearing intracranial human glioblastoma (SF295; U251) xenografts and showed greater activity compared with docetaxel [15].

Ortataxel, another second-generation taxane tested in pre-clinical and clinical studies showed activity in different tumors [16–19] and was reported to be effective also against orthotopically implanted human glioblastoma xenografts [20]. This peculiar feature along with the safety profile that emerged from the phase I studies [19], prompted us to hypothesize the potential therapeutic activity of ortataxel against glioblastoma and subsequently led us to design a phase two study in patients with glioblastoma recurring after surgery and first line treatment.

Materials and methods

Patients

Patients ≥ 18 years with histologically confirmed GBM (World Health Organization [WHO] grade IV astrocytoma) in recurrence/progression after surgery or biopsy, standard radiotherapy and chemotherapy with temozolomide were eligible for the study. Eligible patients had a Karnofsky performance status (KPS) ≥ 60% and adequate hematologic, renal, and hepatic function. Patients who were receiving corticosteroids had to receive a stable or decreasing dose within 5 days prior to registration. Patients with a pre-existing peripheral neuropathy, grade ≥ 2 were not eligible for the study entry. More detailed information are reported in the study protocol (supplementary material). All patients were evaluated before and at regular intervals during their participation in this study. Safety evaluations consisted of medical interviews, recording of adverse events, physical examination, measurement of vital signs, electrocardiograms (ECGs), and laboratory measurements (haematology, chemistry, and urinalysis).

Study design and treatment

This was a randomized, non-comparative phase II study, that included a calibration arm with fotemustine. Patients with GBM at first recurrence and fulfilling the eligibility criteria were randomized with a 2:1 ratio to receive ortataxel or fotemustine. On October 2014, due to the low accrual rate the study was amended, the enrollment of patients in the calibration arm was closed modifying the design to a single arm study. All subsequent information concern the clinical trial protocol as it was carried out after the amendment; data on the patients treated in the calibration arm were not reported in this paper.

The primary objective of the study was to evaluate the efficacy of ortataxel in terms of PFS-6. PFS, overall survival at 9 months (OS-9) after the enrollment, objective response rate (ORR), compliance, tolerability and safety were evaluated as secondary endpoints. The ortataxel schedule used in this study was 75 mg/m^2 i.v. every 3 weeks based on the MTD resulting from the phase I study [19] in 26 patients with refractory solid tumors.

A premedication with ranitidine, diphenhydramine and dexamethasone was administered. Patients were assessed every 3 weeks during the treatment, including physical

examination and KPS. To characterize the safety and tolerability profile of ortataxel, patients were carefully monitored throughout the study. The adverse events (AEs) and serious adverse events (SAEs) were collected according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Disease assessments were performed every 6 weeks after the date of enrollment using the Response Assessment in Neuro-Oncology (RANO) criteria [21]. Study treatment continued until disease progression, unacceptable toxicity, patient or physician decision to discontinue. For patients who discontinued treatment for reasons other than progressive disease, disease assessments were performed every 6 weeks until the first progression. After progression, survival follow-up information were collected via patient medical records, and/or clinic visits every 6 weeks until 9 months from the enrollment, death, loss to follow-up, or patient decision to discontinue participation in survival follow-up.

The protocol was approved by the Competent Authority and the Ethics Committees at the participating sites. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This study is registered with ClinicalTrials.gov, number NCT01989884.

Sample size calculation

The sample size calculation was based on the considerations that a PFS-6 of 20% is of no therapeutic interest, while a PFS-6 of at least 35% is relevant. The type I and type II error probabilities were fixed to 10%, one-sided and 10% (power = 90%), respectively. According to the Simon Optimal model, this phase II study had a two-stage design. At the first stage, if 7 or more patients out of the first 33 included and considered eligible for the per-protocol (PP) population remained alive and progression free after 6 months from enrollment, the total number of patients would be increased to 58, otherwise the study would be stopped for futility. Taking into account a 10% of patients not evaluable for the primary endpoint, it would be necessary to enroll approximately 37 for the first stage and up to 64 for the second stage.

Statistical methods and considerations

PFS-6 was defined as the percentage of patients who were alive and progression free at 6 months after the enrollment. Progression-free survival (PFS) was defined as the time from the date of enrollment up to the date of first progression, second primary malignancy or death from any cause, whichever came first. OS-9 was defined as the percentage of patients who are alive at 9 months after the enrollment. ORR was defined as the percentage of patients who are judged by the investigators to have an objective response (complete or partial response) (CR + PR) as determined by the RANO criteria, achieved within the time from drug administration to progressive disease or end of study.

Efficacy endpoints were assessed in the PP population. The PP population included all patients enrolled in the study who provided informed consent, without major eligibility criteria or study conduction violations, who received at least 2 cycles of treatment (unless interrupted treatment for progressive disease or death) and whose disease is assessed. Compliance analysis was performed according to the intention-to-treat (ITT) population, which included all enrolled patients without major violations of eligibility criteria. Safety analysis was conducted in all patients who received at least one dose of treatment.

Baseline covariate and treatment distributions were summarized using descriptive statistics (mean and standard deviation [STD], minimum and maximum values for continuous variables, and absolute and percentage frequencies for categorical variables). Survival functions were estimated by the Kaplan–Meier method. Survival endpoints were described using median and interquartile range (IQR). The median follow-up was calculated using the reverse Kaplan–Meier method [22]. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary NC).

Results

The Consort flow-chart of patients is depicted in Fig. 1. A total of 40 patients were recruited in the study from 6 centres between November 26th, 2013 and December 12th, 2015. Two patients were excluded from all the analyses due to major violations (one enrolled after second progression, and one no informed consent was signed).

The main characteristics of patients are reported in Table 1. The age ranged from 31.7 to 77.9 years with a mean of 57.7 years (STD 11.4). Most of patients were female (22 [57.9%]) and the KPS was 90% in 47.4% of patients enrolled. Regarding the baseline tumor characteristics all patients had a tumor with histopathological grade 4.

Prior treatments received

After initial diagnosis, all patients underwent to a craniotomy with residual disease in 9 cases (23.7%). Twenty patients (52.6%) underwent an additional operations (19 underwent craniotomy and 1 open biopsy) before study inclusion. After the primary surgery, all patients were treated with radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by 6–12 cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each
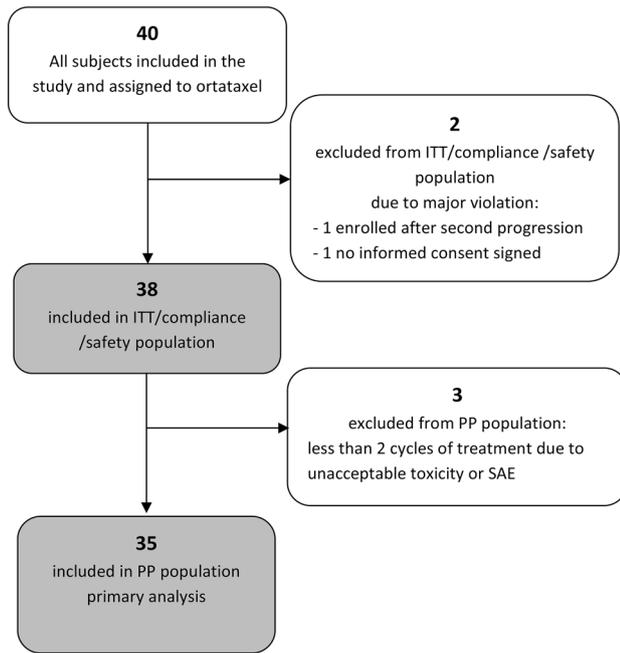
Fig. 1 Consort flow-chart diagram of enrolled patients

28-day cycle)[3], except one that was treated with temozolomide plus tamoxifene. Conformational radiotherapy was performed on all patients, with a mean total irradiated dose of 59.0 Gy (STD 4.3) for a mean duration of 6.2 weeks (STD 2.2). The mean number of chemotherapy cycles was 6.47 (STD 3.04). The best response to the adjuvant treatment was complete response (CR) or partial response (PR) in 5 patients (13.2%), with most presenting stable disease (SD) 24 (63.2%) and a mean duration of chemotherapy treatment of 5.6 months (STD 3.2). The mean time interval between the last cycle of adjuvant treatment to study enrollment was 6.6 months (STD 11.9).

Treatment compliance

All patients enrolled received at least one cycle of the study treatment. Treatment administration delay or dose reduction was registered in 16 (42.1%) patients out of 38. Disease progression was the main reason for treatment interruption which was observed in 30 patients (83.8%) out of the 37 patients who had interrupted treatment before the cutoff date for the analysis (December 2017). One patient was still under treatment and had received more than 50 cycles of ortataxel. More than 50% of patients received at least 3 cycles and 13.2% of patients received at least 10 cycles. For details on number of cycles administered and reasons for discontinuation see Fig. 2.

Table 1 Patients baseline characteristics

	Overall
Number of patients—N	38
Age (years)	
Mean (SD)	57.7 (11.4)
Min–max	31.7–77.9
Sex—n (%)	
Female	22 (57.9)
Male	16 (42.1)
Karnofsky performance status—n (%)	
100	4 (10.8)
90	18 (48.6)
80	5 (13.5)
70	7 (18.91)
60	3 (8.1)
Missing	1
Histopathological grade at diagnosis—n (%)	
3[a]	1 (2.6)
4	37 (97.4)
Residual disease after initial surgery—n (%)	
No	29 (76.3)
Yes	9 (23.7)
Type of radiotherapy—n (%)	
Conformational	38 (100)
Total irradiated dose (Gy)	
Mean (SD)	59.0 (4.3)
Min–max	40.5–66.0
Number of chemotherapy cycles	
Mean (SD)	6.1 (3.3)
Min–max	0.0–13.0
Duration of chemotherapy (months)	
Mean (SD)	5.6 (3.2)
Min–max	1.0–12.1
Missing	1
Best overall response of previous chemotherapy line—n (%)	
CR	3 (7.9)
PR	2 (5.3)
SD	24 (63.2)
PD	8 (21.1)
Unknown	1 (2.6)
Months from last cycle of chemotherapy to enrollment	
Mean (SD)	6.6 (11.9)
Min–max	0.3–65.8
Further surgery—n (%)	
No	18 (47.4)
Yes	20 (52.6)

[a]Astrocytoma evolving in glioblastoma
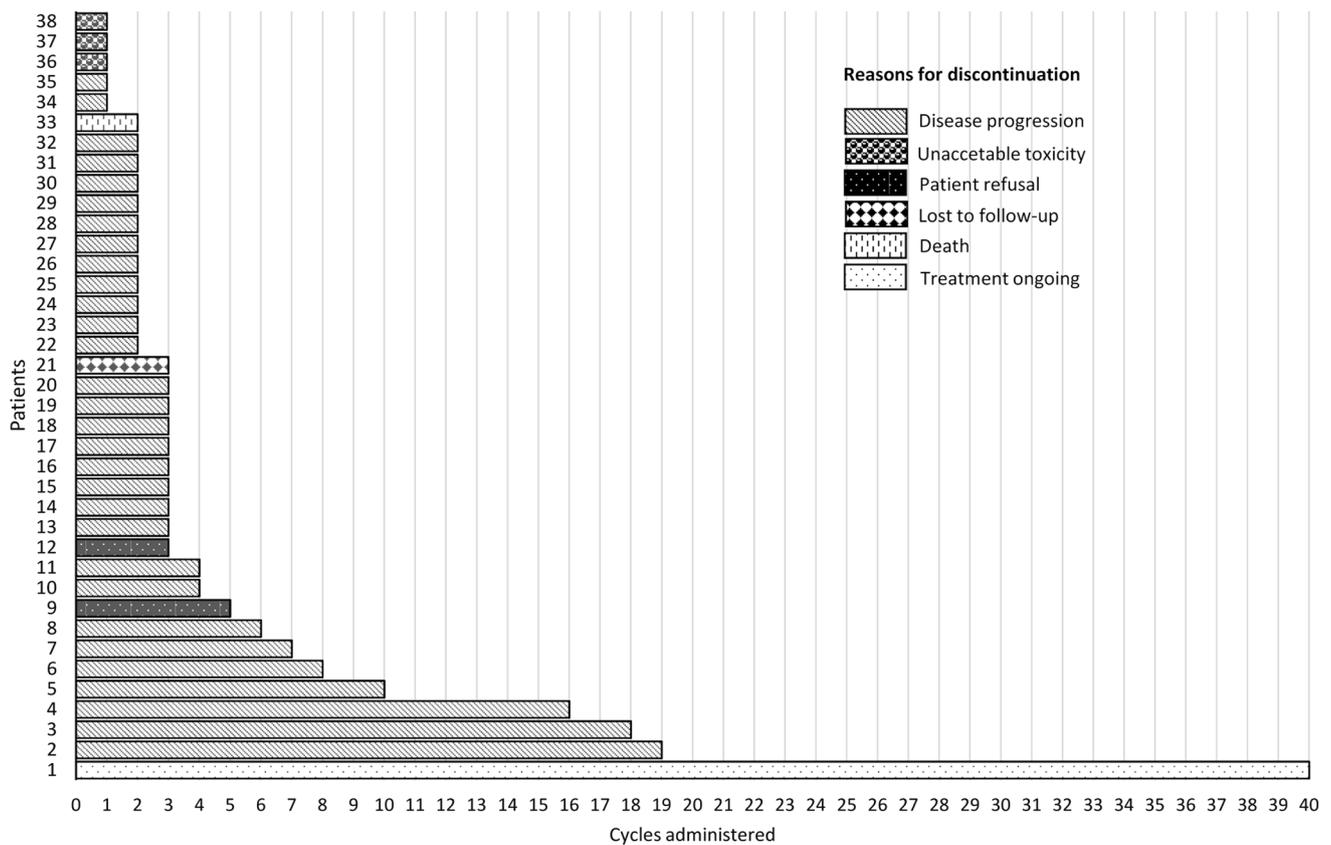
Fig. 2 Number of completed cycles in subject who started treatment and reason for discontinuation

Efficacy

Three patients were excluded from the PP population because they received less than 2 cycles and they interrupted the treatment for unacceptable toxicity. Therefore 35 patients were analyzed for the primary endpoint.

PFS-6 was 11.4%: four patients were alive and progression free at 6 months after the enrollment. One additional patient progressed at 5.5 months with the appearance of a new lesion. However his clinical status was considered stable and therefore the continued the treatment with ortataxel receiving up to 18 cycles until further disease progression. All other patients progressed in a range from 1.0 to 5.5 months from the study entry. The median follow-up was 19.9 months (IQR 12.0–32.0). Median PFS was 1.7 months (IQR 1.4–3.8). Regarding the OS-9, 21 patients out of 35 (OS-9%: 37.8; 95% CI 21.8–53.8) died before 9 months from the enrollment, in a range from 0.99 to 7.70 months from study enrollment. Further 8 patients died before the study closure in a range between 9.5 and 18.5 months from study enrollment. The Kaplan–Meier curve for PFS is depicted in Fig. 3. The best response to treatment was PR in one patient who remained on treatment when the analysis was performed. Nine patients (29.0%) achieved SD.

Even if the overall results of the study were negative, we saw activity in four patients treated for at least 16 cycles. With this in mind, particular attention should be paid to a female, age 43, who underwent a craniotomy with no residual tumor after surgery. After a first disease progression, a further surgery was performed before the study entry. This patient remains on treatment with no evidence of progression in the left frontal lobe target lesion after more than 50 cycles and with no relevant adverse events. One additional patient experiencing stable disease for the target lesions showed the appearance of a new lesion after 7 cycles of treatment with ortataxel. Despite this, the clinician decided to continue ortataxel treatment with the two target lesions –remaining stable for a further 7 months.

Safety

Out of 38 patients, 34 (89.5%) had at least one adverse event. Overall 222 adverse events (AEs) from 34 patients were reported. A relationship with the study drug was reported for 101 AEs. Out of these, 26 events, observed from 17 patients, were grade 3–4 adverse drug reactions and are summarized in Table 2. The most important toxicities were neutropenia, hepatotoxicity and leukopenia that occurred in 5 patients

Fig. 3 Progression-free survival in the per protocol population. Kaplan Meier curve
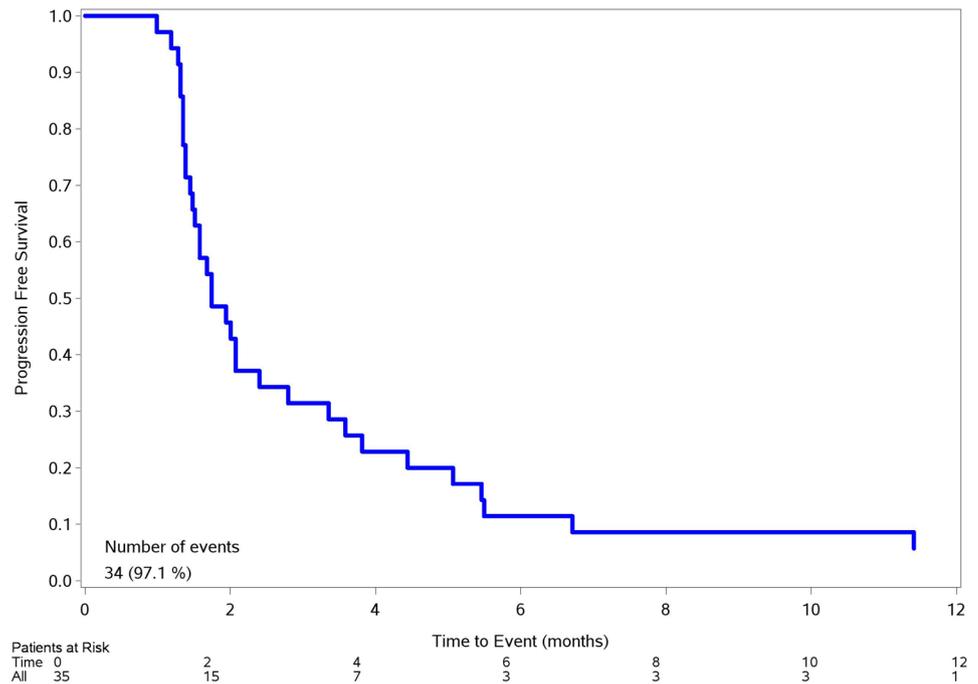
Table 2 Adverse drug reactions to ortataxel (38 patients)

	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G3 + G4 n (%)
Neutropenia	2 (5.3)	0 (0.0)	1 (2.6)	4 (10.5)	5 (13.2)
Lymphopenia	5 (13.2)	1 (2.6)	2 (5.3)	0 (0.0)	2 (5.3)
Leukopenia	6 (15.8)	3 (7.9)	4 (10.5)	2 (5.3)	6 (15.8)
Thrombocytopenia	6 (15.8)	1 (2.6)	0 (0.0)	1 (2.6)	1 (2.6)
Anaemia	10 (26.3)	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	2 (5.3)	2 (5.3)	1 (2.6)	3 (7.9)
Alanine aminotransferase increased	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatotoxicity	4 (10.5)	5 (13.2)	5 (13.2)	0 (0.0)	5 (13.2)
Constipation	2 (5.3)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	1 (2.6)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	6 (15.8)	4 (10.5)	1 (2.6)	0 (0.0)	1 (2.6)
Chills	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasms	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	0 (0.0)	2 (5.3)	0 (0.0)	2 (5.3)
Paraesthesia	4 (10.5)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaphylactic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.6)

(13.2%), 5 patients (13.2%) and 6 patients (15.8%) respectively. No deaths due to toxic events occurred. One SAE, anaphylactic shock was classified as a Suspected Unexpected Serious Adverse Reaction. This SAE was adequately treated with a progressive improvement of hypotension as well as hypoxia until the complete resolution.

Discussion

The present study failed to show significant activity of ortataxel in patients with recurrent GBM relapsing after surgery, radiotherapy and chemotherapy with

temozolomide, as only four patients out of 35 (11.4%) were progression free at 6 months after enrollment. The reason why we tested ortataxel in these patients was its relative good penetration in CNS as shown in the preclinical systems [20]. In particular in mice treated with equitoxic doses of paclitaxel and ortataxel the Area Under the Curve (AUC) in brain was 1.4 and 6.3 $\mu g/ml \times h$, corresponding to 1.2 and 17.5% of the plasma AUC values respectively. Although no data are available on the concentration of ortataxel in human CNS, since the drug is not a substrate of P-gp [17] it probably crosses the blood–brain barrier much more than the other taxanes in human too. Nevertheless we cannot exclude that the concentration of ortataxel achieved in GMB after the dose used were too low to exert antitumor activity. The dose of 75 mg/m^2 of ortataxel used here was derived from a phase I study in patients with tumors differing from GBM without any information about the concentrations reached at the target [19]. On the other hand we know that the evaluation of drug concentrations in the CNS is not easily feasible. Alternatively the low activity of ortataxel could be due to resistance mechanisms related to cellular uptake inhibition to taxanes as a result of tubulin and anti-apoptotic gene mutations as well as the production of survival factors within tumor microenvironment [23].

From a methodological point of view, the applied study design had, as its most important limitation, the absence of a control group. This did not permit the evaluation of biases that could affect the study results. As we stated in the methods, we planned for a calibration arm but due to the low accrual rates we modified the study design from a randomized to a single arm study. An additional study limitation may be the absence of an independent central review of disease assessment in order to minimize the potential detection bias due to the single investigators judgment of disease status.

Regarding the results on ortataxel safety, toxicities were qualitatively similar and quantitatively less than the marketed taxanes, paclitaxel and docetaxel, namely neutropenia, leukopenia, hepatotoxicity, peripheral neurotoxicity, fatigue, diarrhea, nausea, vomiting, constipation, hypersensitivity reaction. It is noteworthy to mention that peripheral neurotoxicity was much less than anticipated with only two cases of grade 3 observed, whereas our phase 1 trial patients previously received only temozolomide. We feel the reason why we observed a lower frequency of toxicities is most likely related to the fact that patients participating in the phase I study were heavily pretreated with bone marrow toxic compounds.

Even if the overall results of the study were negative, we saw activity in some patients as described in "Results" section. In the literature, long-term survivors GBM are reported and molecularly characterized [24]. The methylation of methylguanine-methyltransferase (MGMT) promoter-gene, the isocitrate dehydrogenase (IDH) mutation, lower rates of mutation of p53 and phosphatase and tensin homolog (PTEN) seemed to be associated with a better prognosis. Nevertheless our sample is too small to demonstrate any association between molecular profiles and prognosis. Even so, we have observed some patients with long duration of response to treatment. As such it may be interesting to investigate the molecular characteristics of patients included in our study utilizing next-generation sequencing (NGS) technologies with the aim of identifying potential predictive biomarkers.

Conclusion

This randomized non-comparative phase two study aimed to evaluate the efficacy of ortataxel in patients with glioblastoma recurring after surgery and first line treatment.

The present study did not show clinically significant activity of ortataxel in this setting of patients. Nevertheless, we saw some activity in 11.4% patients that were treated for at least 16 cycles.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest with regard to the research, authorship, and/or publication of this article.

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