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ORIGINAL ARTICLE

Hydroxyurea with or without imatinib in the treatment of recurrent or progressive meningiomas: a randomized phase II trial by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO)

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Abstract
Purpose Hydroxyurea (HU) is among the most widely used salvage therapies in progressive meningiomas. Platelet-derived growth factor receptors are expressed in virtually all meningiomas. Imatinib sensitizes transformed cells to the cytotoxic effects of chemotherapeutic agents that interfere with DNA metabolism. The combination of HU with imatinib yielded intriguing results in recurrent malignant glioma. The current trial addressed the activity of this association against meningioma.
Methods Patients with recurrent or progressive WHO grade I–III meningioma, without therapeutic indication for surgery, radiotherapy, or stereotactic radiosurgery, aged 18–75 years, ECOG performance status 0–2, and not on enzyme-inducing anti-epileptic drugs were randomized to receive HU 500 mg BID ± imatinib 400 mg QD until progression, unacceptable toxicity, or patient's refusal. The primary endpoint was progression-free survival rate at 9 months (PFS-9).
Results Between September 2009 and February 2012, 15 patients were randomized to receive HU + imatinib ($N = 7$; Arm A) or HU alone ($N = 8$; Arm B). Afterward the trial was prematurely closed due to slow enrollment rate. PFS-9 (A/B) was 0/75 %, and median PFS was 4/19.5 months. Median and 2-year overall survival (A/B) rates were: 6/27.5 months; 28.5/75 %, respectively. Main G3-4 toxicities were: G3 neutropenia in 1/0, G4 headache in 1/1, and G3 vomiting in 1/0.
Conclusion The conduction of a study in recurrent or progressive meningioma remains a challenge. Given the limited number of patients enrolled, no firm conclusions can be drawn about the combination of imatinib and HU. The optimal systemic therapy for meningioma failing surgery and radiation has yet to be identified.

Keywords Meningioma · Hydroxyurea · Imatinib · Salvage therapy · Target therapy

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Introduction

Meningiomas are the most common primary central nervous system tumors (CNS) and amount to a third of primary brain tumors. Their incidence is age-related, likely destined to increase. The World Health Organization (WHO) defined three subtypes with different clinical behaviors and histologies according to grading, determined by progressively increasing anaplasia and number of mitotic figures: grade 1 meningiomas (80–90 %) with recurrence rates up to 20 %, atypical or grade 2 (5–15 %) with recurrence rate up to 40 %, and then anaplastic or grade 3 with recurrence rates up to 80 %. Biology and site characterize different clinical courses: from silent incidentalomas to lesions involving eloquent brain areas or rapidly evolving life-threatening masses [1].

Surgery is the treatment of choice whenever feasible in symptomatic patients or in cases with lesions larger than 3 centimeters [2]. The most important risk factors for post-surgical recurrence are the tumor grading and the degree of resection according to Simpson [3]. The role of postoperative radiotherapy in the treatment of meningiomas is still controversial, despite its routine use in clinical practice in this setting. The same holds true to radiosurgery [2].

There is not a standard of care after surgical and/or radiotherapy/radiosurgery failure [4]. Different drugs, including both old chemotherapeutic agents and targeted therapies, such as interferon-alpha, somatostatin analogue, hormonotherapy, imatinib, sunitinib, sorafenib, erlotinib, gefitinib, vatalanib, and the monoclonal antibody bevacizumab [4], were investigated in relapsed meningiomas, without showing consistent efficacy. Accordingly, new therapeutic agents and strategies to improve progression-free survival (PFS) in recurred/progressive disease should be encouraged [1]. HU is the most investigated and widely used drug at time of failure. HU is an oral ribonucleoside reductase inhibitor that can induce apoptosis in meningioma cell cultures and animal models, regardless of WHO grading [5]. It has been evaluated in several small, heterogeneous and often retrospective series, including <60 patients yielding a very low rate of objective response rate (about 6 %) and a median progression-free survival (PFS) of 44–176 weeks [6–17].

Imatinib mesylate is an oral tyrosine kinase inhibitor that targets Bcr–Abl, platelet-derived growth factor receptors (PDGFR), and c-Kit receptor. Meningiomas often overexpress PDGFR-α and β, so they are a potential target for imatinib treatment. Moreover, imatinib increases chemo- and radiosensitivity of different tumor cells in culture such as glioblastoma cells as well as of soft tissue sarcomas and leukemic cells [17–21], suggesting that imatinib may enhance the activity of chemotherapeutic agents used to treat brain tumors. On the other hand, HU, a cytotoxic agent that inhibits DNA synthesis and penetrates the blood–brain barrier, is widely used in relapsed or progressive meningiomas [22]. The combination of HU and imatinib has been investigated in a small phase II trial showing a safe toxicity profile [22]. Accordingly, we conducted a clinical trial to investigate the association of imatinib to HU in relapsed or progressive meningiomas.

Patients and methods

Patients

Patients 18–75 years old with a WHO performance status of 2 or less, adequate hematologic, renal, and hepatic function (total bilirubin < 1.5 × ULN, SGOT and SGPT < 2.5 × UNL, creatinine < 1.5 × ULN), and adequate bone marrow function (ANC > 1.5 × 10^9/L, platelets > 100 × 10^9/L, Hb ≥ 9 g/dL, affected by recurrent or progressive meningioma of any grade, not amenable to surgery, radiotherapy or radiosurgery, were eligible for this trial. Written informed consent was mandatory, and the study was approved by the ethics committees of the participating centers. Exclusion criteria included: optic nerve sheet tumors and neurofibromatosis type II, second malignancies, anti-epileptic treatment with EIAED, brain metastasis, chronic liver disease (i.e., chronic active hepatitis, and cirrhosis), HIV infection, and any significant history of non-compliance to medical regimens.

Study design, treatment, and safety assessment

The primary endpoint of the study was progression-free survival at 9 months from randomization (PFS-9), and PFS was defined as the time between randomization and disease progression or patient's death. The secondary endpoints were: overall survival (OS), defined as the time between randomization and patient's death; overall response rate using MacDonald's criteria; safety, defined as occurrence of toxic event of any grade according to the NCI Common Toxicity Criteria, v. 3.0, as described below. The study was approved by the institutional review board of each participating site; all participants provided written informed consent.

This was an open-label, randomized, phase II clinical trial in which eligible patients were assigned to receive HU 500 mg BID with/without imatinib 400 mg QD. Randomization was centrally performed on a 1:1 basis, stratifying for WHO grade (I vs II–III). Treatment was continued until disease progression, patient's refusal, unacceptable toxicity, or medical decision. In case of disease progression, in absence of toxicity ≥grade 2, the protocol allowed to escalate imatinib dose to 600 mg. Treatment after completion of the study was at the discretion of the investigator.

If the patient experienced a grade 2 non-hematologic toxicity, study drugs were withheld until the toxicity had resolved to <grade 2. Imatinib and hydroxyurea could be resumed at the same daily dose after toxicity resolution. In case of grade 2 toxicity recurrence, imatinib had to be withheld until the toxicity had resolved to <grade 2, and the daily dose should be thereafter reduced to 300 mg once daily. Hydroxyurea had to be withheld until the toxicity had resolved to <grade 2, and the daily dose should be reduced to 400 mg BID.

If the patient experienced grade 3 toxicity, study drug should be withheld until the toxicity has resolved to <grade 2. The daily dose of imatinib should be reduced to 300 mg once daily. Hydroxyurea should be withheld until toxicity downgrading to <grade 2 and the daily dose

should be reduced to 400 mg BID. If the patient experienced grade 4 toxicity, study drugs must be discontinued definitely.

In case of grade 3/4 hematological toxicity, study drugs should be withheld until the toxicity had resolved to ≤grade 2. If resolution occurred within 2 weeks, imatinib treatment could be resumed at the same dose and hydroxyurea should be resumed at the dose of 400 mg BID.

The screening assessments had to be performed 15 days before treatment start and included: physical examination, ECOG performance status and vital signs assessment, brain magnetic resonance imaging (MRI) scan, hematology, and blood chemistry. During treatment, all patients underwent tumor assessment every 12 weeks by contrast enhanced MRI.

Statistical analysis

Based on the outcome figures reported in the literature, a PFS-9 of 50 % was expected with HU [4–6]. Since there is no universally accepted or standard endpoint for phase II trials in meningiomas, this endpoint, as well as any other, may be disputable, but we retained PFS-9 as an adequate surrogate of activity to be assessed in a phase II trial. A PFS of 65 % in experimental group was defined as the minimum threshold of interest. With a one-sided $\alpha = 0.20$ and $\beta = 0.20$, assuming a 10 % of ineligible/non assessable patients, 2 years of accrual, and 1 year of follow-up, 38 meningiomas per arm would be enrolled.

The primary analysis and all secondary efficacy analyses were performed on the ITT population. Due to premature interruption of the study, only descriptive analyses were performed. Kaplan–Meier method was used to calculate and plot PFS and OS.

Results

Due to difficult recruitment, only 15 patients from five centers were enrolled into the trial in the study period, between September 2009 and February 2012. Accordingly, the trial was prematurely concluded. Seven patients were randomized to receive HU + imatinib (Arm A) and eight to receive HU alone (Arm B). Baseline patients' characteristics are summarized in Table 1. Despite the small sample size, the two groups were well balanced in terms of age, tumor grade, number of prior surgeries, and median time from diagnosis. There were more males and patients with ECOG PS 1 in group A. Radiation therapy (radiotherapy, radiosurgery or both) was used in all but four patients (1/3), external beam radiation therapy in 6/5, and radiosurgery in 1/3 patients. No patients received prior systemic chemotherapy.

Table 1 Patients' characteristics

	Group A	Group B
Age (year)		
Median	68	68.5
Range	28–73	50–79
Gender no. (%)		
Female	3 (43)	5 (63)
Male	4 (57)	3 (38)
ECOG performance status score no. (%)		
0	1 (14)	3 (38)
1	5 (71)	2 (25)
2	1 (14)	3 (38)
Grade		
1	1 (14)	1 (13)
2	4 (57)	5 (63)
3	1 (14)	0 (0)
Unknown	1 (14)	2 (25)
Time from diagnosis (months)		
Median	86	73.5
Range	26–172	15–252
Previous surgery		
Median	3	2
Range	1–4	1–6

The median number of cycles of HU + imatinib and HU administered was (A/B) 4 (range 2–7) and 11 (range 4–14). All arm A patients had disease progression within 6 months from treatment start, while PFS-9 was 75 % in arm B. Two arm B patients remain progression-free at 33 and 56 months. Median PFS was 4.0 months in arm A and 19.5 months in arm B.

Six arm A and five arm B patients died of disease progression, while one arm A patient was alive at 33 months, and three arm B patients are alive at 22, 41 and 56 months from treatment start. Median and 2-year OS were 6 months and 28.5 % in arm A and 27.5 months and 75 % in arm B (Table 2).

All patients were assessed for response. No objective response was observed in either arm. Best response was stable disease in 4 arm A and 8 arm B patients for a median time of 5.5 (range 4–6) and 19 (range 4–55) months, respectively (Table 2).

All patients received the assigned treatment. The median number of cycles of HU + imatinib and HU administered was (A/B) 4 (range 2–6) and 11.5 (range 2–24), respectively. No patient is currently on treatment: Two arm B patients completed the treatment as per protocol design, while treatment was interrupted due to disease progression in seven arm A and four arm B patients, patient's refusal in one arm B, and toxicity in one arm B patient. No treatment-related death occurred. Main treatment-related toxicities are reported in Table 3. Two patients required imatinib dose

Table 2 Activity and efficacy analyses summary

	Arm A HU + imatinib	Arm B HU
Best response		
Partial response	0	0
Stable disease	4	8
Progression-free survival (PFS)		
Median PFS (month)	4	19.5
9-Month PFS	0 %	75 %
Overall survival (OS)		
Median OS (month)	6	27.5
2-year OS	28.5 %	75 %

Table 3 Treatment-related toxicity

Adverse event no. (%)	HU + imatinib (Arm A)		HU (Arm B)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Neutropenia	–	1 (14 %)	–	–
Headache	–	1 (14 %)	–	1 (12.5 %)
Vomiting	–	1 (14 %)	–	–
Rash	1 (14 %)	–	–	–
Infection	–	–	2 (25 %)	_
Asthenia	1 (14 %)	–	–	–

reduction to 300 mg/day, for three cycles due to G2 rash and for one cycle due to G4 headache, vomiting and asthenia, respectively.

Discussion

The present study did not meet its primary endpoint and failed to prove any activity of the association of imatinib + HU. In fact, no patient was free from progression at 9 months, no objective response was observed, and only four patients had a short-lasting stable disease in the experimental arm. Surprisingly, PFS-9 was 75 % for patients treated with HU alone.

When this trial was designed, no universally accepted primary endpoint for this disease was available. More recently, PFS-6 was recommended as appropriate benchmark for trial design [3]. PFS-6 was 29 % for arm A and 75 % for arm B. Consistently, disease control rate and stable disease duration were longer and also survival seems to be better in the single-agent arm (median OS: 6 and 27.5 months; 2-year OS: 28.5 and 75 %). Due to the slow accrual, the trial was prematurely closed. Despite the small number of patients enrolled, this is the only prospective randomized study that evaluated the activity of the association of imatinib + HU and of single-agent HU. The small sample size of the trial and some unbalanced baseline characteristics across arms, like the presence of one patient with grade 3 meningioma in arm A or of a patient who did not receive prior irradiation in arm B, may in part justify the worse outcome of patients receiving imatinib + HU as compared to those treated with single agent. However, study design facilitates the interpretation of results as compared to single-arm trials. In fact, a prior single-arm phase II trial prospectively evaluated efficacy of HU and imatinib combination on 21 patients, reporting outcomes in terms of OS (66 months for grade I and 20.9 for grade II–III), PFS-6 (62, 87.5 and 46 % for grade I, II and III meningiomas, respectively) and SD (67 %) [22]. Remarkably, in this trial, the combination of imatinib with hydroxyurea was only modestly active for this indication. Imatinib was also prospectively assessed as single agent in 22 patients with recurrent meningiomas yielding a PFS-6 of 29 %, a median PFS of 2 months, and SD in 47 % of patients [12]. Altogether, these data are consistent with our findings and do not suggest any role for imatinib in combination with HU in the therapeutic management of meningiomas.

Similarly, previous studies on cytotoxic chemotherapy for refractory meningiomas also failed to show any benefit. Several trials have explored a variety of agents, all with disappointing results [23–26]. The only exceptions were early reports suggesting that HU was active in recurrent meningiomas [5, 7, 25–27]. Conversely, recent retrospective series reported a very limited benefit with 35–43 % of SD and a PFS-6 of only 3 % [14, 15]. Our study seems to suggest some activity of HU. However, due to the premature conclusion of the trial and to the small number of patients, no firm conclusion can be drawn, and the role of this agent in the therapeutic management of meningiomas remains controversial.

Since various aberrant signaling pathways have been identified in meningiomas [28], several targeted molecular therapies have been studied in clinical trials [28–35] mainly with disappointing results in meningioma patients. Promising results (PFS-6 44–86 %) from small retrospective series were reported with bevacizumab, but toxicity, including hemorrhage, grade 4 intestinal perforations, and grade 5 pneumonia/sepsis, was remarkable [32, 33]. Confirmatory single-arm phase II trials are ongoing (NCT01125046, NCT00972335). PTK-787 was tested in a prospective trial on 25 grade II/III patients yielding an intriguing PFS-6 of 54.4 % and a median PFS of 7 months [34].

Results of a phase II trial on sunitinib, a tyrosine kinase receptor inhibitor targeting both VEGF and PDGF receptors, were recently reported [35]. Patients with meningioma (30 atypical and 6 anaplastic) were treated with 50 mg/day of sunitinib yielding a PFS-6 of 42 % of, a median PFS of 5.2 months and median OS of 24.6 months. However, a

concerning rate of intratumoral hemorrhage was reported, including 1 grade 5, 2 grade 3, and 1 grade 4. Furthermore, 1 grade 3 and 1 grade 4 thrombotic microangiopathy and 1 grade 3 gastrointestinal perforation were observed. Altogether, the results of these trials are difficult to interpret due to the retrospective nature or to the single-arm design of the studies, which are subject to selection bias.

A more promising novel, marine-derived, antineoplastic agent, trabectedin, approved and routinely used in advanced soft tissue sarcoma and ovarian cancer was investigated in a preclinical study by Preusser et al. [36]. This study revealed a strong cytotoxic activity of trabectedin in various meningioma cell lines and clinical benefit associated with radiological reduction in edema in one heavily pretreated 64-year-old patient with trabectedin. Trabectedin-associated reduction in brain edema and corticosteroid in malignant meningioma seems to be similar to what has been reported with bevacizumab in malignant glioma.

In conclusion, the optimal systemic therapy for meningioma failing surgery and radiation has yet to be identified due to the small number of prospective clinical trials available in the literature and to the heterogeneity of outcomes across trials, likely due to selection bias, which strongly suggests adopting the randomized design to improve results interpretability. Other important methodological issues to take into account are the adequate sample size, the use of standardized response criteria, and stratification based on prior treatment and tumor grade. Hopefully, the inclusion of patients in well-designed, prospective, cooperative clinical trials may bear some improvement in the therapeutic management of this orphan disease.

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