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Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series

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Background: Grade IV malignancies of the brain, such as glioblastoma multiforme (GBM), are associated with a dismal prognosis. Autocrine and paracrine loops of platelet-derived growth factor (PDGF) signaling, as well as other signal transduction pathways, have been postulated to play a role in glioblastoma transformation, and molecules involved in these pathways can potentially serve as targets for therapeutic inhibitory agents. Imatinib, an inhibitor of PDGF receptors α and β, as well as other selected tyrosine kinases, is indicated for treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST). Unfortunately, imatinib, as with many conventional chemotherapeutic agents, has limited efficacy as monotherapy in GBM. In preclinical studies, the chemotherapeutic agent hydroxyurea is demonstrated to have cytotoxic effects additive with imatinib.

Patients and methods: We tested the combination of hydroxyurea and imatinib in 30 grade IV progressive GBM patients refractory to chemo- and radiotherapy. All 30 patients were evaluable after a median 19 weeks observation time.

Results: Combination therapy with imatinib and hydroxyurea resulted in a 20% response rate, including complete and partial responses. Patients experiencing response or stable disease yielded a combined clinical benefit rate of 57%. Median time to progression was 10 weeks and median overall survival was 19 weeks. Three patients continue to survive on combination therapy, with the shortest duration being 106 weeks. Six-month and 2-year progression-free survival rates were 32% and 16%, respectively.

Conclusion: The efficacy results, combined with findings that imatinib and hydroxyurea were well tolerated, suggest that this combination shows promise as therapy for GBM.

Key words: efficacy, glioblastoma multiforme, hydroxyurea, imatinib, PDGFRs, safety

Introduction

Glioblastoma multiforme (GBM), the highest grade (IV) of malignant gliomas, is relatively rare, occurring at a rate of seven per 100 000 tumors, yet is common among brain tumors. GBM can progress from lower grade astrocytic gliomas or arise *de novo*. Regardless of origin, grade IV GBM is associated with an extremely poor prognosis [1, 2]. Even after optimal treatment with function-saving surgical resection followed by both radiation and chemotherapy, the median survival of patients newly diagnosed with GBM is slightly more than a year [3]. Trials investigating new therapies for GBM generally involve relapsed or progressive patients. A summary of eight phase II trials with cytotoxic or cytostatic drugs for treatment of recurrent GBM at a single center resulted in a 6-month progression-free survival rate of 15% and a median overall survival rate of 30 weeks [4]. Together, these observations suggest that the vast majority of glioblastoma patients will experience fatal disease progression within the first 2 years.

Preclinical investigations have focused on gaining insight into the molecular basis for glioblastoma oncogenesis with the aim of identifying potential therapeutic targets. There is considerable support for the hypothesis that platelet-derived growth factor (PDGF) autocrine signaling plays a role in the transformation of gliomas [5–12]. This has prompted the notion that inhibition of PDGF receptors (PDGFRs) might directly arrest GBM by interrupting an autocrine growth cycle [13, 14]. Alternatively, inhibition of PDGFRs may affect GBM tumor growth by indirect mechanisms relating to the tumor stroma or vasculature [15–17].

Imatinib is a small molecule inhibitor of PDGFRα and β, as well as KIT, ABL, BCR-ABL and ARG tyrosine kinases [18, 19]. Imatinib is indicated for treatment of chronic myelogenous leukemia [20–23] and unresectable or metastatic gastrointestinal stromal tumor (GIST) [24–26].

Preliminary trials with imatinib as monotherapy for treatment of GBM have been conducted [27]. A multi-center phase II study of imatinib in 51 patients with recurrent GBM, obtained

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confirmed partial responses in two patients treated with imatinib 600 mg and in one patient treated with imatinib 800 mg for longer than 10 months. Prolonged tumor stabilizations for longer than 6 months were reported in one patient taking imatinib 600 mg and in four patients taking imatinib 800 mg. An earlier phase I trial examined 40 patients with malignant primary brain tumors, including 24 with GBM, treated with imatinib [28]. Among 31 evaluable patients, 14 maintained stable disease and of those, four maintained stability for as long as 24 weeks.

The reasons underlying this level of efficacy with imatinib monotherapy for treatment of GBM are not clearly understood. Interestingly, a recent phase II trial investigating the epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, as monotherapy for recurrent GBM, yielded modest results in a subpopulation of patients [29]. Together, results from these trials with targeted kinase inhibitors for recurrent/relapsed GBM patients suggest that perhaps such agents may be expected to exhibit efficacy as monotherapy in only subsets of patients. Whether related to tumor complexity or variability, these results raise the possibility that a combinatorial approach may be more beneficial.

Preclinical studies provide evidence that imatinib increases the chemo- or radiosensitivity of glioblastoma cells as well as of soft tissue sarcomas and leukemic cells in culture [30–34], suggesting that imatinib may enhance the activity of chemotherapeutic agents used to treat GBM. Hydroxyurea, a cytotoxic agent that inhibits DNA synthesis, is widely used in cancer therapy and penetrates the blood–brain barrier [35, 36]. This patient series investigated the combination of imatinib and hydroxyurea in patients with progressive temozolomide-resistant GBM.

Patients and methods

Thirty GBM patients with disease progression, refractory to radiation therapy and chemotherapy (temozolomide plus nitrosourea), and with no other treatment option available to them, were included in this series (Figure 1, Table 1). Only patients with World Health Organization (WHO) tumor classification grade IV tumors diagnosed by two different independent neuropathologists participated. Disease progression, according to Southwestern Oncology Group (SWOG) criteria, was documented by two magnetic resonance imaging (MRI) scans within 6 weeks and 3 months.

The median age of patients was 44 years (Table 2). All 30 patients had radiation therapy between 50 and 60 Gy following surgical resection (Figure 1, Table 1). Patients in the series then had at least two chemotherapy cycles with temozolomide plus nitrosourea, except one patient who had three. It was mandatory that surgical and radiation options were excluded by a neurosurgeon and radiotherapist before inclusion in this series. One patient experienced a rapid progression during irradiation combined with temozolomide chemotherapy, which was documented by MRI scan 4 weeks after the start of treatment. Systemic treatment was changed to nimustine hydrochloride (ACNU) with continued radiotherapy. Following significant progression, this patient entered the investigational series less than 3 months from the time of confirmed diagnosis. Twenty-eight patients had a second progression of GBM and one patient was experiencing a third progression of GBM upon entering the study. All patients received dexamethasone in a median dose of 12 mg/day (range 8–24 mg/day). Immunohistochemical examinations could not be performed in the majority of cases. Co-morbidities of patients participating in this series are listed in Table 3. Patients with co-morbid hypertension were all well treated for the condition and the co-morbid condition of diabetes was not attributed to steroid induction in any patient. Twenty-six patients received enzyme-inducing anticonvulsants, four patients received non-enzyme-inducing anticonvulsants, and three patients were exposed to both (Table 3). Eastern Cooperative Oncology Group (ECOG) performance status at the start of therapy was 0, 1 or 2.

Treatment costs were paid by the patient or by a clinic fund, and in eight cases by insurance after efficacy was indicated. Patient consent for participation was confirmed by a third person in each case (Table 1).

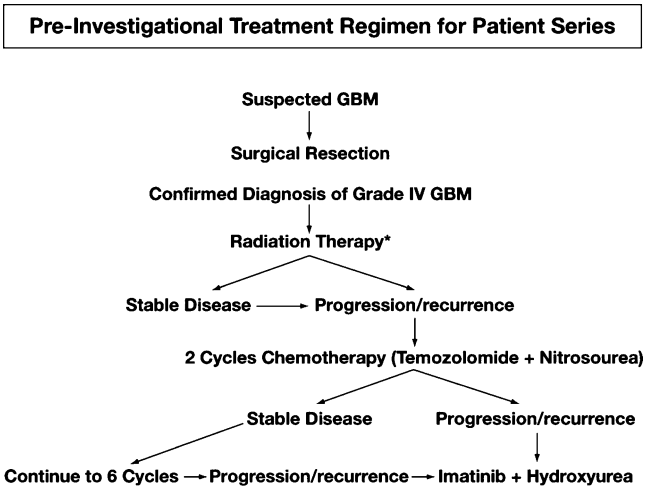

Figure 1. Diagram of treatment regimen for patients in this series prior to initiation of imatinib plus hydroxyurea therapy. The point at which Patient 27, with rapidly progressing disease, entered the investigational series after failing radiation plus temozolomide and ACNU therapy less than 3 months from confirmed diagnosis is indicated by *.

Table 1. Inclusion criteria

Age 16 years or older
Confirmed informed consent
Confirmed histopathology of WHO grade IV glioblastoma multiforme
Prior radiotherapy with 50–60 Gy, no radiotherapy treatment option
Prior temozolomide and nitrosourea containing chemotherapy
No neuro-surgical treatment option
Confirmed tumor progression (SWOG criteria) according to MRI scan
No pregnancy and no breastfeeding
No other malignant disease
ECOG performance status 0, 1 or 2
Adequate renal, liver and bone marrow function
Ensured weekly blood cell count
Ensured MRI scan every 6 weeks
No evidence of non-compliance

Table 2. Summary of patient demographics

Sex	25 male, 5 female
Median age, years (range)	44 (16–71)
Median duration between confirmed diagnosis and imatinib plus hydroxyurea therapy, months (range)	12 (2–57)

Table 3. Comorbidities and concurrent anticonvulsive drug type: individual patient series

Patient no.	Comorbidities	EIADS	NEIADS
1	None	No	Yes
2	None	Yes	No
3	None	Yes	No
4	None	Yes	Yes
5	None	Yes	No
6	None	Yes	No
7	None	Yes	No
8	None	Yes	No
9	Diabetes mellitus[a]	Yes	No
10	None	Yes	No
11	None	Yes	No
12	None	Yes	No
13	None	Yes	No
14	None	Yes	No
15	None	Yes	No
16	Diabetes mellitus[a]	No	Yes
17	None	No	Yes
18	None	Yes	No
19	Hypertension[b]	Yes	No
20	None	Yes	No
21	None	Yes	No
22	Hypertension[b]	Yes	No
23	Hypertension[b]	Yes	No
24	None	Yes	No
25	None	Yes	Yes
26	None	Yes	No
27	None	No	Yes
28	None	Yes	No
29	Diabetes mellitus[a]	Yes	No
30	None	Yes	Yes

[a]Not steroid induced.

[b]Well treated.

EIADs, enzyme-inducing anticonvulsive drugs; NEIADS, non-enzyme-inducing anticonvulsive drugs.

Patients were treated with imatinib 400 mg once daily and hydroxyurea 500 mg twice daily and were monitored by clinical examination, weekly blood cell counts, and MRI every 6 weeks for as long as patients remained clinically stable on treatment. SWOG criteria were used for evaluation of objective tumor response to treatment. All scans were evaluated by a radiologist and reviewed by the investigator. Scans were subsequently blinded for independent radiological evaluation by Gregory Sorensen (Massachusetts General Hospital, Charlestown, MA, USA). Clinical benefit was defined to include both partial and complete responses as well as stable disease lasting at least 3 months. Patients with tumor growth, detected by MRI, that did not satisfy SWOG criteria of progressive disease and did not lead to a decrease in performance status (no increased steroid dose required) were treated with imatinib 600 mg/day with no change in hydroxurea dose.

Results

Thirty patients were evaluable for safety and efficacy after a median observation time of 19 weeks (range 4–148 weeks) (Table 4). One patient reached complete response lasting 12 months and five patients reached a partial response in MRI scan lasting a median of 3 months (range 6 weeks to 25 months). A series of MRI scans from Patients 11 and 14, listed in Table 4, illustrates the extent of responses to imatinib plus hydroxyurea from baseline (documented progression) throughout several months of therapy. Patient 14 achieved a partial response and Patient 11 reached stable disease (Figure 2). The response rate, including partial and complete responses, was 20% (Table 5). Eleven patients reached stable disease for a median of 6 months (range 3–32 months). With regard to the inclusion criteria and the expected outcome of these patients, clinical benefit was defined as disease stabilization for a minimum of 3 months or more. Patients with stable disease, combined with responding patients, yielded a clinical benefit rate of 57%. Thirteen patients progressed without response or stable disease. Patient 11 progressed after a 142-week period of stable disease and died 6 weeks later and Patient 16 progressed after a 108-week period of stable disease and is still alive 8 weeks later, having another stable disease period 6 weeks after treatment start with liposomal pegylated doxorubicin. Two other patients remain alive without progression for 122 and 106 weeks, respectively. Among these patients, Patient 14 had a partial response lasting 12 weeks and then maintained stable disease and Patient 22 had a durable stable disease. Patient 4 maintained stable disease for 104 weeks before progressing to death. Twenty-five patients finally died with progressive disease. The median time to progression for all 30 patients was 10 weeks. Six-month and 2-year progression-free survival rates for all patients in the series were 32% and 16%, respectively (Figure 3A). Median overall survival was 19 weeks and the shortest and longest survival durations were 4 and 148 weeks, respectively (Figure 3B).

There was no treatment interruption and there were no grade 3 or 4 toxicities. Four patients experienced grade 2 edema and six patients experienced grade 2 abdominal pain. One patient had grade 2 neutropenia (Table 6). Two patients died of pulmonary embolism, one patient having a partial response according to MRI scan and one patient with stable disease. Both events are considered unrelated to treatment with imatinib and hydroxyurea since thrombosis and thrombo-embolic complications are frequent occurrences in progressive glioblastoma [37–39].

Discussion

The current standard for newly diagnosed GBM, when feasible, is surgical resection followed by radiotherapy and, more recently, by chemotherapy. In a recent phase II trial, 573 newly diagnosed GBM patients were randomized to receive radiotherapy or radiotherapy plus concomitant or adjuvant temozolomide, a recently available alkylating agent with antitumoral efficacy in GBM [40]. Eighty-four per cent of patients in this trial had had previous surgical resection. The combination of temozolomide and radiotherapy resulted in a 2-year survival rate

Table 4. Progressive glioblastoma responses to treatment with imatinib and hydroxyurea: individual patient series

Patient no.	Age	Sex	Type of primary surgery	Months from diagnosis to imatinib plus hydroxyurea	Best response	Duration of response (weeks)	Status (as of January 2005)
1	35	M	Incomplete	10	PR	13	Dead, PD
2	38	M	Complete[a]	11	PR	NS	Dead, PE
3	44	F	Incomplete	17	CR	52	Dead, PD
4	65	M	Complete[a]	17	SD	104	Dead, PD
5	29	F	Incomplete	9	SD[b]	26	Dead, PD
6	35	M	Incomplete	8	SD	NS	Dead, PE
7	45	M	Incomplete	9	PD	None	Dead, PD
8	19	M	Biopsy only	15	SD	29	Dead, PD
9	47	M	Incomplete	13	PR	10	Dead, PD
10	32	F	Incomplete	11	PD	None	Dead, PD
11	39	M	Complete[a]	18	SD	142	Dead, PD
12	32	M	Complete[a]	4	PD	None	Dead, PD
13	61	M	Incomplete	11	PD	None	Dead, PD
14	33	M	Complete[a]	8	PR[b]	122 (12 weeks partial response then stable disease)	Alive, SD
15	42	M	Incomplete	17	PD	None	Dead, PD
16	33	M	Complete[a]	57	SD[b]	108	Alive, PD
17	57	M	Incomplete	3	PD	None	Dead, PD
18	38	M	Incomplete	8	PD	None	Dead. PD
19	65	M	Complete[a]	12	SD	33	Dead, PD
20	16	M	Complete[a]	24	PD	None	Dead, PD
21	44	M	Complete[a]	12	PD	None	Dead, PD
22	44	M	Incomplete	9	SD[b]	106	Alive, SD
23	60	F	Complete[a]	20	PD	None	Dead, PD
24	71	M	Incomplete	18	PD	None	Dead, PD
25	42	M	Complete[a]	15	PD	None	Dead, PD
26	71	M	Complete[a]	17	SD	14	Dead, PD
27	60	M	Incomplete	2	SD	25	Dead, PD
28	52	M	Complete[a]	15	PR	6	Dead, PD
29	58	F	Incomplete	17	PD[b]	None	Dead, PD
30	57	M	Incomplete	11	SD	26	Dead, PD

[a]Macroscopically complete, not histologically confirmed R0.

[b]Imatinib 600 mg/day.

NS, not stated because death not related to tumor; PD, progressive disease; PE, pulmonary embolism; CR, complete remission; PR, partial response; SD, stable disease.

of 26% compared with 10% for radiotherapy alone. Median overall survival was 15 months for patients treated with the combination and 12 months for patients treated with radiotherapy alone. Trials investigating new therapies for GBM generally involve relapsed or progressive patients. Temozolomide was tested in two separate trials involving hundreds of GBM patients at first relapse, with or without prior chemotherapy [41, 42]. Six-month progression-free survival rates of 18% and 21% were obtained.

This investigational series of treatment-refractory GBM patients treated with imatinib plus hydroxyurea yielded a clinical benefit rate, defined as either tumor response (partial or complete response) or as stable disease lasting at least 3 months, in 57% of patients. Among 30 patients, five patients achieved partial and one patient achieved complete response that lasted approximately 3 months for a total response rate of 20%. The 6-month progression-free survival rate was 32% and the 2-year progression-free survival rate was 16%. These results are comparable with published studies in investigational trials with recurrent or relapsed GBM patients [1, 4, 41, 42].

Combination therapy with these two agents was well tolerated with no grade 3 or 4 toxicities. Two patients died of pulmonary embolism, a well-known complication with progressive GBM

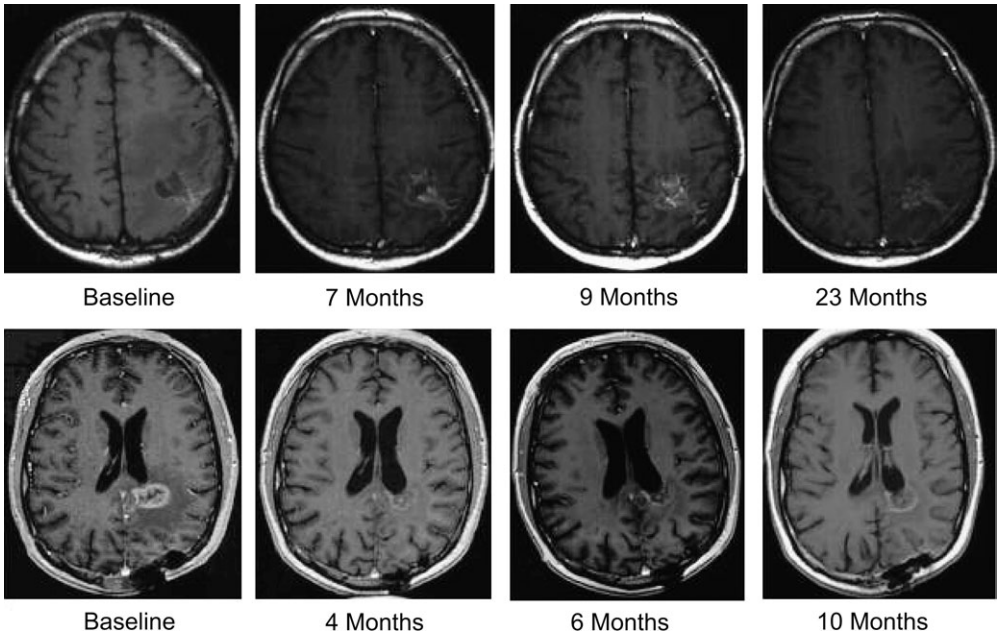

Figure 2. Magnetic resonance images from Patient 11 (top panel) achieving stable disease and Patient 14 (bottom panel) achieving partial response followed by stable disease for the indicated times after imatinib therapy for glioblastoma multiforme (GBM). In each patient, GBM can be seen in the left hemisphere at baseline. Gadolinium T_1 contrast medium was used during imaging.

Table 5. Summary of efficacy and survival of imatinib plus hydroxyurea therapy for progressive glioblastoma multiforme

Response rate (including partial and complete)	20%
Clinical benefit rate (including partial and complete response plus stable disease)	57%
6-month progression-free survival rate	32%
2-year progression-free survival rate	16%
Median time to progression	10 weeks

[37–39]. A relationship between pulmonary embolism and treatment was considered unlikely.

Because the patients in this study were relatively young (median 44 years) and with good initial performance status, it is likely that the proportion of secondary GBM was higher in this population compared with a more elderly population [43]. Nevertheless, previous studies have observed no difference in the prognostic significance between primary and secondary grade IV GBM among age-matched patients. This suggests that the prognosis among patients in this series was likely to be similar [44]. Moreover, while one of the youngest patients attained disease control for a period, the other never responded and neither patient is among the longest-lived subset. It is possible that a subset of patients in this series may have been predisposed to respond to PDGFR inhibition and that this sensitivity was contingent on whether the GBM was primary or transformed [5–12, 43]. Future studies may resolve this issue.

Several possible explanations could underlie the positive results obtained with the combination of hydroxyurea and imatinib compared with single-agent imatinib. Although the extent to which imatinib penetrates the blood–brain barrier in GBM is unknown, hydroxyurea, by virtue of its ability to traverse the blood–brain barrier, may enhance the crossing of imatinib by inhibiting activity of ABCG2 ATP or P-glycoprotein, multidrug transporters with affinity for imatinib [45, 46]. Imatinib also inhibits ABCG2 activity, indicating the potential for a complex cumulative interaction of hydroxyurea and imatinib that elevates and prolongs central nervous system concentrations of both agents. During combination therapy imatinib may reach target cells somehow differently than in the single-agent setting, possibly by an adjuvant-type interaction [47].

It should also be noted that the majority of patients in this series were treated with enzyme-inducing anticonvulsants. The effect of these agents on the pharmacokinetics and pharmacodynamics of imatinib plus hydroxyurea in GBM patients is presently unknown but is a factor to consider with respect to the mechanism of action of this combination.

In the brain, imatinib may engage its potential array of antitumor mechanisms that may include direct or indirect effects on tumor growth through inhibition of PDGFRs. PDGFR signaling has been demonstrated to directly promote glioblastoma cell survival and growth in culture as well as in living mice [8–11], whereas inhibition of PDGFR signaling suppresses cell growth [7, 14]. The hypothesis that aberrant PDGFR signaling may be involved in glioblastoma transformation is consistent with observations that human glial tumors overexpress PDGFRs compared with normal brain tissue [6, 48].

In addition to the direct role that PDGFR signaling may play in the proliferation of brain tumor cells, there is also the possibility that indirect mechanisms of PDGFR signaling contribute to brain tumor growth. Inhibition of PDGFRs expressed on pericytes associated with blood vessel endothelial cells might suppress brain tumor growth via an anti-angiogenic mechanism [49]. Furthermore, expression of PDGF and PDGFRs on tumor

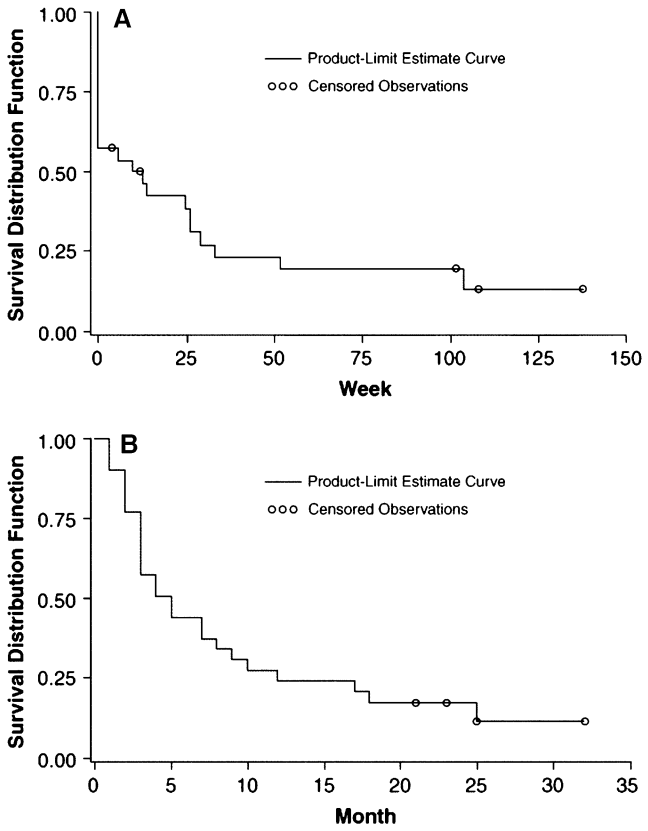

Figure 3. Survival of 30 progressive glioblastoma multiforme (GBM) patients treated with imatinib and hydroxyurea. (**A**) Progression-free survival (**B**) and overall survival.

Table 6. Summary of adverse events of therapy with imatinib and hydroxyurea

6 patients with grade 2 abdominal pain	Patients 4, 5, 6, 8, 9 & 22
4 patients with grade 2 edema	Patients 15, 16, 22 & 29
1 patient with grade 2 neutropenia	Patient 1

stromal cells can also affect tumor growth by regulating interstitial fluid pressure or other tissue factors that influence uptake of drugs into tumors [50].

Another possible mechanism of action of imatinib, which is likely to be independent of PDGFRs, is suggested by evidence that in isolated cells in culture, imatinib sensitizes transformed cells to the cytotoxic effects of chemotherapeutic agents that interfere with DNA metabolism, or more recently reported, to radiotherapy [30, 33, 34]. In this series of patients, cytotoxicity would not be expected to play a major role in defeating GBM because all patients were refractory to nitrosourea. However, combination therapy with imatinib may have potentiated the chemosensitivity of tumor cells [31, 32, 34].

While the precise mechanisms and interactions relevant to imatinib efficacy in this series of patients are not clear, the observations indicate that the combination of hydroxyurea and imatinib shows promise as a safe and effective therapy for a subpopulation of otherwise treatment refractory GBM patients. This is accomplished either through the induction of response or disease control with concomitant long-term survival in this subset of patients. Trials are underway to evaluate further this combination as treatment of GBM, as well as to characterize better the subpopulation of responding patients to perhaps select for those most likely to benefit from the combination in the future.

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