

## Myelosuppression in patients benefiting from imatinib with hydroxyurea for recurrent malignant gliomas

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**Abstract** Reports suggest reasonable efficacy and minimal myelosuppression from combination imatinib and hydroxyurea for recurrent malignant glioma. We retrospectively reviewed 16 patients treated with this regimen who were evaluable for toxicity; 14 were also evaluable for response. The incidence of grade 3–4 hematologic toxicity was 25%. The best radiographic response, by Macdonald criteria, was partial response (PR) in three patients (21%), stable disease (SD) in four (29%), and progressive disease (PD) in seven (50%). One patient with a PR developed therapy-limiting hematologic toxicity on day 19 of treatment, progressing to grade 4 on day 64, and persisting until death on day 127 despite discontinuing both drugs. Another patient with PR and two of four patients with SD also developed grade 3 hematologic toxicity. All patients with grade 3–4 hematologic toxicity had disease control (PR or SD) as best radiographic response, whereas none with PD suffered grade 3–4 hematologic toxicity. Combining imatinib with hydroxyurea is effective in some patients

with malignant glioma. However, myelosuppression can persist for months after discontinuing the regimen, precluding further chemotherapy. Disease control may also correlate with hematologic toxicity ( $p = 0.08$ ), suggesting that glioma and marrow stem cells may share a common sensitivity to this chemotherapy regimen.

**Keywords** Chemotherapy · Glioblastoma · Hydroxyurea · Imatinib · Myelosuppression · Stem cells

### Introduction

Glioblastoma multiforme (GBM) is an incurable and aggressive brain tumor with limited chemosensitivity and a median survival of approximately one year. Imatinib (Gleevec, previously named STI-571; Novartis, East Hanover, New Jersey) inhibits platelet-derived growth factor receptor (PDGFR) as well as other targets and has been used in clinical trials for recurrent GBM because of the frequent co-amplification of PDGF and PDGFR in gliomas [1]. However, imatinib monotherapy is generally ineffective for recurrent GBMs, with objective responses in less than 5% of patients and a 6-month progression-free survival (6mPFS) rate of 3–16% [2, 3]. In an attempt to improve efficacy, two recent trials combined imatinib with hydroxyurea, a ribonucleoside diphosphate reductase inhibitor that disrupts DNA synthesis. Objective responses were observed in 9–20% of patients with recurrent GBM, with disease control (partial response [PR], complete response [CR], or stable disease [SD]) achieved in 51–57% of patients [4, 5]. The 6 mPFS rate was 27–32%, likely superior to the efficacy of imatinib [2, 3] or hydroxyurea [6] monotherapy as well as the DNA alkylators temozolomide (6mPFS 18–21%) [7–9] or carmustine (6mPFS

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17.5%) [10]. In addition, reported myelosuppression was minimal. For example, using the NCI Common Terminology Criteria for Adverse Events (CTC), no grade 4 (life-threatening) hematologic toxicity was reported in either trial, and grade 3 (severe) hematologic toxicity ranged from 0% [5] to 15% [4]. The first patient at Memorial Sloan-Kettering Cancer Center (MSKCC) had a partial radiographic response associated with dramatic clinical improvement. However, he also developed prolonged grade 4 neutropenia, anemia, and thrombocytopenia that precluded further treatment with myelosuppressive chemotherapy. Therefore, with the first patient as the index case, we conducted a retrospective study to examine hematologic toxicity in our patients receiving this regimen because the toxicity data reported in clinical trials that concentrate on severity (grade) may not describe duration or outcome. In addition, as the regimen also induced a partial radiographic response in our index patient, we sought to assess whether toxicity correlated with efficacy.

## Patients and methods

We retrospectively reviewed records of all patients at MSKCC treated with a combination of imatinib and hydroxyurea for recurrent malignant gliomas from June 2004 to January 2007. This regimen was first used at MSKCC following presentation of the efficacy and toxicity data at the 2003 American Society of Clinical Oncology [11] and the 2004 Society for Neuro-Oncology [12] meetings. We specifically examined hematologic toxicity as well as best radiographic response. All patients were considered evaluable for toxicity. Patients were also considered evaluable for efficacy if they received at least one cycle (defined as four weeks) of treatment, and had a baseline as well as a follow-up MRI scan with gadolinium enhancement. Efficacy was determined by the best radiographic response defined with reference to the previous scan, and was determined using Macdonald criteria as CR, PR, SD, or progressive disease (PD) [13]. This study was approved by the Institutional Review Board at MSKCC.

## Results

### Index case

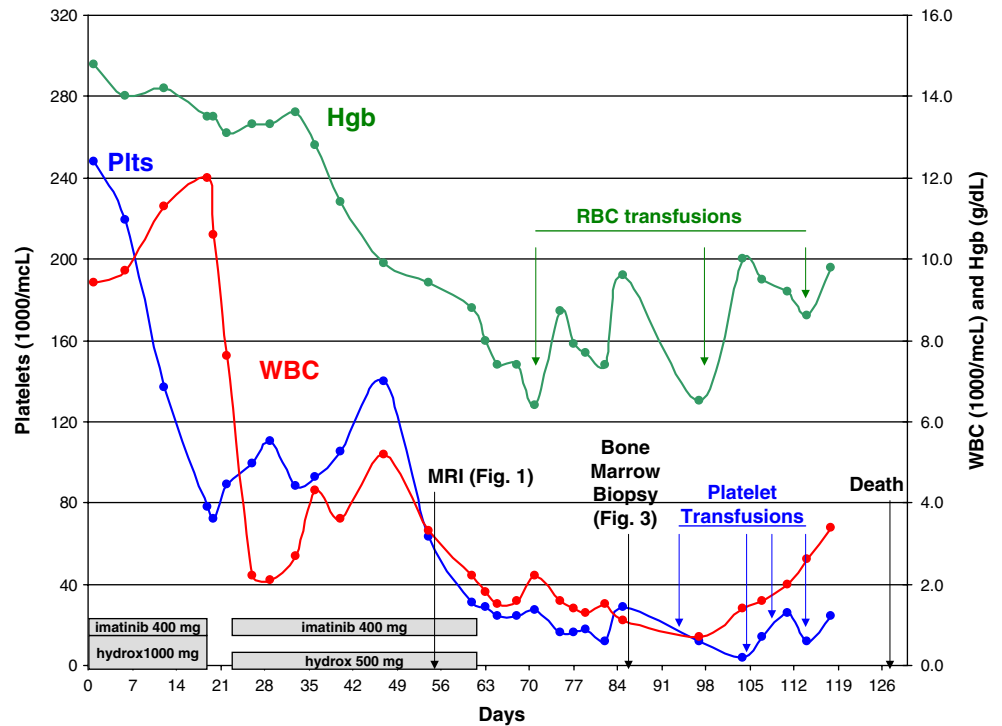
A 58 year-old right-handed man was diagnosed with a left temporal lobe GBM following a seizure. After receiving phenytoin initially, his antiepileptic regimen was changed to levetiracetam which he continued through the course of his illness. He was otherwise asymptomatic with a normal

physical and neurological examination. He underwent a gross total resection of the tumor followed by concurrent external beam radiation therapy (60 Gy) with temozolomide at 75 mg/m<sup>2</sup> body surface area (BSA) [14]. He completed concurrent radiation and temozolomide without complications, but rapid disease progression necessitated a change in chemotherapy. The tumor progressed again after one cycle of carmustine (150 mg/m<sup>2</sup> BSA) and then one cycle of enzastaurin (LY317615; Lilly, Indianapolis, Indiana), a protein kinase C-beta inhibitor [15]. He then initiated treatment with imatinib 400 mg daily and hydroxyurea 500 mg twice daily [4, 5]. After 19 days, the platelet count dropped from 248 (1000/mcL) at baseline to 78 (Fig. 1). Therapy was interrupted for three days, and the platelet count recovered to 89. Full dose imatinib (400 mg daily) was restarted, but the dose of hydroxyurea was reduced by half to 500 mg once daily. A brain MRI performed 55 days after initiating imatinib + hydroxyurea revealed PR (Fig. 2). He also exhibited substantial clinical improvement with resolution of aphasia and hemiparesis, and he returned to work full time. However, the pancytopenia worsened such that after 61 days, the WBC decreased to 2.2 (1000/mcL) and the platelets to 31. Both imatinib and hydroxyurea were discontinued, and the patient received numerous blood and platelet transfusions and growth factor support with both granulocyte colony stimulating factor and erythropoietin. After 85 days, the myelosuppression had not improved substantially, prompting a bone marrow biopsy (Fig. 3) which revealed severe panhypoplasia and fatty replacement with minimal hematopoietic activity and cellularity of less than 10%. He was dependent on transfusions and growth factor support. He developed worsening neurological disability, and a brain MRI performed on day 98 revealed progression of disease (not shown). During the next several weeks, the blood counts remained low, although there was a slight increase in the WBC to 3.4 from a nadir of 0.7. He died from tumor progression with continued myelosuppression 127 days after initiating imatinib and hydroxyurea.

### All patients

A total of 16 patients received combination treatment and were evaluable for toxicity; 14 (including the index case) were also evaluable for best response. There were nine men and seven women. Ten patients had GBM, two had anaplastic astrocytoma (AA), two had anaplastic oligodendroglioma (AO), one had anaplastic oligo-astrocytoma (AOA), and one had gliosarcoma (GS). The age range was 20 to 69 with median age of 47 years. These patients had received from one to four standard or investigational prior chemotherapy agents, with a median of three (Table 1). As

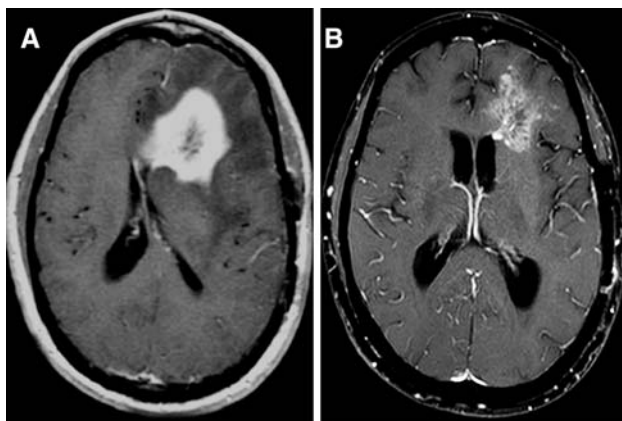
**Fig. 1** Peripheral blood counts after initiation of imatinib 400 mg daily and hydroxyurea 1000 mg daily (500 mg bid). Platelet count (1000/mcL) is shown in blue with the scale on the left axis; WBC (1000/mcL) in red and hemoglobin (g/dL) in green are shown with the scale on the right axis



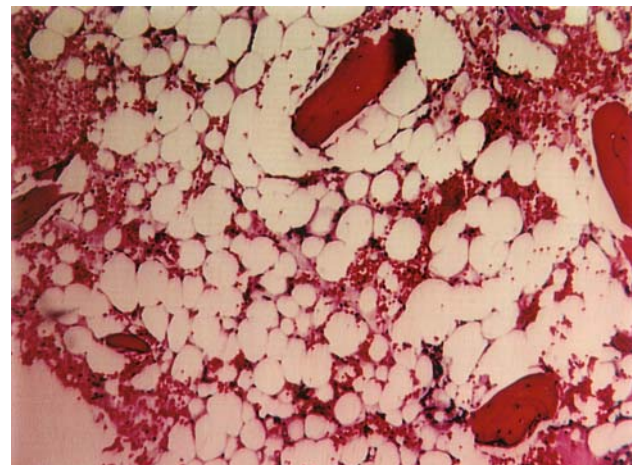
published previously, [4] the starting dose of hydroxyurea for all 16 patients was 500 mg bid. The starting dose of imatinib for the 13 patients not taking hepatic enzyme inducing antiepileptic drugs (EIAEDs) such as phenytoin, phenobarbital, primidone, carbamazepine, and oxcarbazepine was 400 mg qd. In one of the three patients taking EIAEDs (Table 1, case 12), the starting dose of imatinib was 500 mg bid [4]. The remaining two patients on EIAEDs both started imatinib at 400 mg qd; one of these (Table 1, case 13) escalated to 500 mg bid after two cycles, and the other (Table 1, case 16) discontinued both drugs after three weeks of treatment because of leg edema. The

number of four week cycles of imatinib/hydroxyurea therapy ranged from 0.6 to 9.5 (median 2.1) for all patients.

The index case described above was the only patient who developed grade 4 hematologic toxicity, treated with a combination of packed red blood cell (PRBC) and platelet transfusions as well as granulocyte-colony stimulating factor (GCSF) support. Three patients (20%) developed grade 3 hematologic toxicity, necessitating PRBC transfusions in two patients and GCSF support, erythropoietin support, platelet transfusions, and reduction of hydroxyurea



**Fig. 2** Brain MRI obtained at baseline (A) and 8 weeks after initiating imatinib and hydroxyurea (B) demonstrating a partial radiographic response



**Fig. 3** Bone marrow biopsy obtained 12 weeks after initiation of imatinib and hydroxyurea, demonstrating aplastic marrow with trilineage acellularity

**Table 1** Individual patient characteristics, responses and toxicities

Case	Age	Histology	Prior chemotherapy	Number of cycles of imatinib/hydroxyurea therapy	Grade 3–4 hematologic toxicity	Intervention	Best response	Duration of grade 3–4 hematologic toxicity (days)	EIAED (yes/no)	Medication list at start of therapy
1 (index case)	58	GBM	temozolomide, carmustine, enzastaurin	2.1	anemia, leukopenia, thrombocytopenia	PRBC, Plt, GCSF, erythropoetin	PR	107	No	levetiracetam, sulfamethoxazole/trimethoprim, dexamethasone, pantoprazole, levofloxacin
2	59	GBM	carmustine, temozolomide, celecoxib, gefitinib	2.9	anemia	PRBC	SD	9	No	levetiracetam, valproic acid, paroxetine, atorvastatin, amlodipine/benazepril, atenolol, esomeprazole, alprazolam
3	32	AA	temozolomide, carmustine, enzastaurin	1.3	none	none	SD	not applicable	No	sulfamethoxazole/trimethoprim, dexamethasone, pantoprazole, olanzapine
4	47	GBM	temozolomide, lomustine	2.0	none	none	PD	not applicable	No	None
5	43	GBM	temozolomide, carmustine, GW572016	2.3	none	none	PD	not applicable	No	levetiracetam, dexamethasone
6	57	GBM	temozolomide, temozolomide + isotretinoin	6.3	leukopenia, neutropenia, thrombocytopenia	PRBC, GCSF, hydroxyurea dosage reduction and cessation	SD	129	No	levetiracetam, clonazepam, escitalopram
7	62	AO	temozolomide	3.6	none	Stopped therapy	PR	not applicable	No	doxazosin, atorvastatin
8	42	GBM	temozolomide, cilengitide, carmustine	2.3	none	none	PD	not applicable	No	levetiracetam
9	42	GBM	temozolomide, carmustine, rapamycin, erlotinib	1.6	none	none	PD	not applicable	No	levetiracetam
10	31	GBM	temozolomide, acutane, carmustine	1.1	none	none	PD	not applicable	No	dexamethasone, gabapentin, dapsone, famotidine
11	47	GBM	temozolomide	9.5	neutropenia	hydroxyurea dosage reduction	PR	84	No	valproic acid, levetiracetam, topiramate
12	59	AOA	carmustine, temozolomide, accutane, bevacizumab	1.2	none	none	PD	not applicable	Yes	phenytoin, levetiracetam, topiramate, dexamethasone, sulfamethoxazole/trimethoprim, levofloxacin, citalopram, methylphenidate
13	69	AA	temozolomide	5.7	none	none	SD	not applicable	Yes	oxcarbazepine, paroxetine, valsartan, simvastatin, aspirin, glipizide
14	47	GBM	temozolomide, bevacizumab, irinotecan	1.6	none	none	PD	not applicable	No	levetiracetam, sulfamethoxazole/trimethoprim, prednisone
15	50	GS	temozolomide, carmustine, gefitinib,	<1	none	none	not evaluable	not applicable	No	dexamethasone, sulfamethoxazole/trimethoprim, zolpidem, morphine
16	20	AO	lomustine, carmustine	<1	none	none	not evaluable	not applicable	Yes	carbamazepine, levetiracetam, pantoprazole

Abbreviations: GBM, Glioblastoma Multiforme; GS, Gliosarcoma; AA, Anaplastic Astrocytoma; AO, Anaplastic Oligodendroglioma; AOA, Anaplastic Oligo-astrocytoma; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; PRBC, Packed Red Blood Cell transfusion; Plt, Platelet transfusion; GCSF, Granulocyte-Colony Stimulating Factor; EIAED, hepatic enzyme inducing antiepileptic drug

**Table 2** Patient characteristics

Pathology	10 GBM; 2 AA, 2 AO; 1 AOA; 1 GS
Gender	9 men; 7 women
Age	Median = 47 (20–69)
# Prior chemotherapy agents	Median = 3 (1–4)
Grade 3 hematologic toxicity	19% (3 / 16)
Grade 4 hematologic toxicity	6% (1 / 16)
Best radiographic response	CR 0; PR 3; SD 4; PD 7
Response rate (CR + PR)	21% (3 / 14)
Disease control rate (CR + PR + SD)	50% (7 / 14)

Abbreviations: GBM, Glioblastoma Multiforme; GS, Gliosarcoma; AA, Anaplastic Astrocytoma; AO, Anaplastic Oligodendroglioma; AOA, Anaplastic Oligo-astrocytoma; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease

dose in one patient each. The median duration of toxicity for these four patients was 96 days (range 28–129).

Best radiographic responses included three patients with PR, four with SD, and seven with PD. No CR was seen. The total objective response rate (CR + PR) was therefore 23%, and the disease control rate (CR + PR + SD) was 54% (Table 2).

## Discussion

Reported toxicity of imatinib monotherapy in patients with glioma included grade 3–4 myelosuppression in 10–15% [2, 3]. In patients with chronic myelogenous leukemia (CML) toxicity is more severe, with a 47% incidence of grade 4 neutropenia and a 29% incidence of thrombocytopenia in one trial [16]. There is a report of a 46 year-old woman with chronic phase CML treated with imatinib who developed pancytopenia with hypoplastic marrow [17]. However, the hematologic toxicity may be more severe during treatment with CML than glioma because of the low fraction of normal stem cells in the marrow at baseline [18]. Hydroxyurea is also associated with myelosuppression. A retrospective study of 101 children with sickle cell disease treated with long-term hydroxyurea demonstrated a 5% incidence of myelosuppression [19].

We report overall grade 3–4 hematologic toxicity of 25% of patients (4/16). This may be higher than the incidence reported previously. For example, one published trial of combination imatinib and hydroxyurea therapy for glioma reported no grade 3 or 4 toxicities [5] and the other reported a 15% incidence of grade 3 hematologic toxicity but no grade 4 hematologic toxicity [4]. However, it should be noted that our sample size is small, leading to a 95% confidence interval (4–46%) that overlaps with the 15% reported previously. Our cohort was slightly more heavily

pre-treated than those in prior reports, one of which limited enrollment to patients who received temozolomide or nitrosourea but no other prior chemotherapy, [5] and the other did not limit prior therapy with a median of 2 prior regimens [4]. However, development of toxicity among our patients did not appear related to the number of prior chemotherapy regimens (median 3, range 1–4 for all patients), as this was not different between those who developed hematologic toxicity (median 2.5, range 1–4) and those who did not (median 3, range 1–4). In addition, hematologic toxicity developed early in the course of treatment when it occurred, and median time to development of initial hematologic toxicity (29 days, range 7–101) was shorter than the median duration of therapy (46 days, range 18–160) for patients who did not develop hematologic toxicity. Therefore, it is unlikely that development of myelosuppression was caused by a longer duration of treatment.

Table 1 lists concomitant medications for all patients during imatinib/hydroxyurea therapy. The one patient treated with the higher dose of imatinib because of concurrent EIAED therapy did not develop hematologic toxicity. There are no obvious differences in the medications taken by patients who developed grade 3–4 hematologic toxicity and those who did not, including other potentially myelosuppressive drugs such as sulfamethoxazole/trimethoprim, phenytoin, dapsone, valproic acid, and carbamazepine. It should also be noted that the index case was on phenytoin, but only for the peri-operative period at initial diagnosis of GBM, and his anticonvulsant regimen was changed to levetiracetam six months prior to initiating imatinib/hydroxyurea therapy. Nevertheless, drug-drug interactions and myelosuppressive effects of other medications cannot be excluded completely as interacting third variables.

Further analysis of our results reveals that all four patients with grade 3–4 hematologic toxicity had disease control (SD in 2, PR in 2) as their best radiographic response. None of the patients with PD developed hematologic toxicity. These observations suggest an association between disease control and grade 3–4 hematologic toxicity ( $p = 0.08$ , Yates chi-square). The only other patient with PR as best response stopped therapy because of severe fatigue, but developed grade 2 neutropenia during treatment. If this patient is incorporated into the analysis, a stronger association emerges ( $p = 0.03$ ). These results suggest that the combination of imatinib and hydroxyurea may have a synergistic effect on glioma growth as well as suppressing hematopoiesis. The observed association between marrow suppression and disease control may point to a shared but as yet undescribed activity against both bone marrow and glioma stem cells. Recent evidence of radioresistance amongst populations of CD133-positive brain cancer stem cells also suggests the importance of

targeting stem cells in achieving tumor control [20, 21]. It is possible that in a subset of patients treated with imatinib/hydroxyurea therapy, stem cells within the bone marrow as well as the glioma itself are targeted resulting in concomitant marrow suppression and tumor control. In vitro studies of this chemotherapy regimen on the CD133 positive subset of glioma cells and marrow stem cells could further explore this finding. Finally, in a patient with CML, reinfusion of peripheral stem cells during imatinib administration allowed continued treatment despite treatment-induced marrow aplasia [18]. It remains unknown whether similar treatment would allow continued treatment of patients with glioma experiencing favorable response to imatinib and hydroxyurea.

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