Imatinib is active in glioblastoma multiforme expressing platelet-derived growth factor receptor

Imatinibe é ativo no glioblastoma multiforme com expressão do receptor do fator de crescimento derivado de plaquetas

Artur Katz1, Carlos Henrique Barrios2, Rober Abramoff3, Sergio Daniel Simon4, Rene Cláudio Gansl5, Jaques Tabacof6, Fabiana Viola7

ABSTRACT

Objective: To report on 15 patients with recurrent anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) previously treated with standard therapies and, then, treated with imatinib.

Methods: Fifteen consecutive patients with recurrent AA or GBM, positive immunostaining for the PDGF-alpha and progression on previous standard therapies (surgery, radiation and chemotherapy with temozolomide) were treated with imatinib (400 mg/day), administered until progression or unacceptable toxicity. Results: One patient achieved a confirmed partial response that lasted for 15 months. In addition, two patients had disease stabilization for eight and 19 months. Treatment was well tolerated and no patient had to be removed due to adverse events. Conclusions: Imatinib seems to be safe and active in patients with high grade astrocytic tumors that express the PDGF-alpha receptor. Based on these results, we initiated phase II trial of high-dose imatinib (800 mg/day) in patients with recurrent AA or GBM.

Keywords: Astrocytoma/drug therapy; Brain neoplasms/drug therapy; Glioblastoma/therapy; Piperazines/therapeutic use; Receptors, platelet-derived growth factor

INTRODUCTION

High-grade astrocytic gliomas, including anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM), are the most frequent primary central nervous system (CNS) tumors in adults. When feasible, maximal surgical resection followed by radiation therapy remains the standard treatment for patients with AA and GBM(1-2). Adjuvant chemotherapy is increasingly utilized and may improve median survival in these patients. Imatinib mesylate, a selective inhibitor of the platelet-derived growth factor receptor (PDGFR), is an orally active medication that inhibits the tyrosine kinase activity of the PDGF-alpha receptor (PDGFR-a). In preclinical studies, PDGF-alpha expression has been detected in human gliomas and glioblastoma cell lines (2). In this report we describe the clinical experience of 15 patients with recurrent AA or GBM positive for PDGF-alpha who were treated with imatinib.
survival by one to three months\(^{(3-4)}\). Unfortunately, most patients with AA or GBM relapse after initial therapy. Palliative chemotherapy is commonly used in the treatment of these patients, but the only encouraging results documented with modern criteria were seen with temozolomide\(^{(5)}\). This oral alkylator produces objective responses in up to 35% of patients with relapsed AA or GBM. Other chemotherapeutic agents or combinations with reported activity in AA or GBM, such as carmustine (BCNU) or procarbazine, lomustine and vincristine (PCV), have less favorable toxicity profiles and also provide modest results.

In recent years, there has been an increasingly greater understanding of the molecular pathways, leading to the development of primary CNS tumors\(^{(6)}\). One of the seminal findings was the correlation between genetic changes and clinical behavior of some tumors. The epidemiology of GBM showed there are two distinct subgroups of the disease. Approximately 20% of patients develop GBM from a previously existing lower-grade astrocytic tumor. In approximately 80% of patients, who are typically older than those with secondary GBM, the disease is diagnosed de novo, in its primary form. It was demonstrated that primary and secondary GBM arise through distinct genetic pathways\(^{(7)}\).

One of the most frequent molecular changes described in gliomas to date is the overexpression of platelet-derived growth factor (PDGF) and its receptors\(^{(8)}\). PDGF functions as homodimers or heterodimers of two different 30-kDa chains (A and B) linked by disulfide bonds. Recently, two other PDGF chains (C and D) were described\(^{(9)}\). Two PDGF receptor chains (alpha and beta) have been described to date. These molecules function as homodimers or heterodimers, and they are members of the type III family of protein-tyrosine kinase receptors. PDGF binding to its receptors leads to receptor phosphorylation and subsequent activation of intracellular signaling pathways important for cancer proliferation and survival. The overexpression of members of the PDGF signaling pathway is an early event in low-grade astrocytic tumors and is found in approximately 25% of GBM patients\(^{(10)}\).

Given the role of PDGF signaling pathway in glioma biology, PDGF receptor inhibition emerged as a therapeutic target in Oncology\(^{(11)}\). Among the strategies that may be used to inhibit the PDGF signaling pathway, small-molecule tyrosine kinase inhibitors represent a logical and convenient step. Imatinib (formerly STI-571) is an orally active inhibitor of the BCR-Abl tyrosine kinase, the gene product of the Philadelphia chromosome found in chronic myelogenous leukemia\(^{(12)}\). Imatinib is also active against two other oncoproteins with kinase activity, namely the PDGF receptor and kit. Imatinib inhibits both PDGF alpha and beta receptors\(^{(13)}\). In a preclinical model, imatinib inhibited the growth of U343 and U87 human glioma cell lines implanted into the brains of nude mice\(^{(14)}\). In this model system, the growth inhibition promoted by imatinib was due to the abrogation of PDGF receptor phosphorylation.

Additional studies are necessary in view of the lack of effective treatments for patients with relapsed AA and GBM, lack of preclinical rationale for the use of imatinib in these diseases, and lack of safe track record of imatinib in Oncology.

**OBJECTIVE**

To investigate the activity of imatinib in the treatment of patients who had progressed after receiving standard therapy for high-grade astrocytic gliomas

**METHODS**

We report on 15 consecutive patients with relapsed AA or GBM, who had their treatment initiated at the Medical Oncology Department of the Hospital Israelita Albert Einstein (HIAE), in São Paulo, Brazil. One patient was referred and subsequently treated in Porto Alegre, Rio Grande do Sul, Brazil, by two of the co-authors. Written informed consent was obtained from each patient entering the study. The study was approved by the appropriate ethics review boards and followed the recommendations of the Declaration of Helsinki for biomedical research involving human subjects and the guidelines for good clinical practice.

Pathologic diagnosis was confirmed in all cases at the laboratory of HIAE, and all patients had astrocytic glioma grade III or IV, according to the World Health Organization (WHO) classification. All patients had been previously treated with surgery and external-beam radiation therapy. In addition, all patients had already been treated with temozolomide as adjuvant or palliative intent. No patients received other types of chemotherapy. All subjects had adequate bone marrow, renal and hepatic functions, and no other serious morbidities.

Immunohistochemistry was performed in all cases, always in the same laboratory. No attempt was made to quantify the level of protein expression in tumor specimens, which were reported as positive or negative for PDGF receptor immunoreactivity. Immunohistochemistry for kit was not performed.

Imatinib (Glivec\(^{6}\), Novartis, Brazil) was administered to all patients at the initial dose of 400 mg per day. All patients underwent regular clinic visits, and magnetic resonance imaging (MRI) scans were performed as deemed necessary by the attending physician. Imatinib was continued until unacceptable toxicity, clinical
or radiographic disease progression, or the patient’s decision to interrupt treatment. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. Objective responses were defined according to the criteria set forth by MacDonald et al. Partial responses were confirmed by a second MRI scan, performed at least four weeks later. Time to disease progression was calculated from the start of imatinib treatment until the date on which progression was first documented.

RESULTS
Fifteen patients were treated with imatinib. The median age was 62 years, and 80% of patients were male. Nine patients were aged over 45 years, and six were younger. One patient had AA, and 14 had GBM. Immunohistochemistry was positive for PDGF receptor-alpha in 14 patients, and negative in one of the patients with GBM.

Among the six patients who were younger than 45 years, one had a partial response, and two had stable disease as their best response to treatment. The partial response occurred in a 19-year-old female patient with GBM (Figure 1). The other two patients, who had GBM, had disease stabilization for eight and 19 months, respectively. One of these two patients achieved a minimal clinically significant response (19-month duration), but the adoption of objective criteria led us to classify this response as stable disease. One of the nine older patients with GBM also had disease stabilization for eight months or over. Therefore, a total of three patients had stable disease as their best response (two among the younger age group and one among the older). The patient with AA was a 38-year-old male and did not respond to treatment. All other patients with GBM had disease progression upon reevaluation.

Treatment with imatinib was well tolerated. There were no cases of grade 3 or 4 toxicity. No dose reduction was necessary, and no patient had to be removed from treatment due to imatinib toxicity. In all cases, treatment discontinuation was due to disease progression.

DISCUSSION
Several lines of evidence point to the pathogenic role played by the PDGF pathway in gliomas. Human gliomas frequently co-express PDGF and PDGF receptors – a finding that suggests the existence of autocrine loops of activation. Mice transfected with a retrovirus coding for the PDGF B-chain developed brain tumors, typically GBM. Hamsters implanted with spheroids containing a wild-type GBM cell line that co-expresses PDGF B-chain and PDGF-alpha receptors died within 21 days; in contrast, the implantation of the same cell line transfected with a dominant-negative mutant form of the PDGF A-chain extended average survival to 80 days. In nude mice, intratumoral injection of a peptide that inhibits ligand binding to PDGF receptors abrogates the growth of U118 glioma cell line xenografts in a dose-dependent manner. All these experiments suggest that PDGF and its receptors play a role in glioma biology, and that these molecules are potential targets for therapeutic intervention.

There is evidence that PDGF signaling is also involved in angiogenesis. High-grade gliomas, especially GBM, are highly vascular tumors. Tumor endothelial vessels in high-grade gliomas overexpress the PDGF-beta receptor. In addition, PDGF seems to upregulate the secretion of vascular endothelial growth factor (VEGF) by glioma cell lines. VEGF is a potent mitogen for endothelial cells, and its production seems to correlate with histological progression of anaplastic and oligodendrocytic tumors. Furthermore, some studies have suggested that an increased VEGF production is associated with a worse prognosis in patients with low-grade and high-grade astrocytic tumors. It is thus conceivable that PDGF inhibition may also interfere with angiogenesis.

Other investigators and institutions are currently evaluating the role of imatinib in the treatment of adult and pediatric patients with gliomas. Imatinib...
has produced a transient partial response in a 14-year-old girl with a metastatic pilocytic astrocytoma that was refractory to other treatments\(^{(20)}\). In that case, immunohistochemistry was performed on tumor specimens obtained two and seven years prior to imatinib treatment. In both specimens, PDGF-alpha and PDGF-beta receptor expression was negative. In addition, Abl and kit expression were negative. Interestingly, however, was the fact that tumor endothelial cells stained positive for the PDGF-beta receptor. This finding was confirmed in tumor specimens from 19 other patients with pilocytic astrocytomas that were tested by the same investigators. The authors of this case report discuss the possible effect of imatinib on the tumor vasculature and suggest further study of this drug in children with refractory pilocytic astrocytomas.

Recently, investigators from the European Organization for Research and Treatment of Cancer reported the preliminary findings of a phase II study of imatinib in patients with recurrent GBM\(^{(29)}\). A total of 51 patients were recruited from nine European institutions. Imatinib was administered until progression at the daily dose of 600 mg or 800 mg in two cohorts of patients, who had prior exposure to radiation (n = 50) and chemotherapy (n = 33). Two patients had confirmed partial responses that lasted for eight months for one patient and more than 18 months for the other. In addition, prolonged (six to 11 months) tumor stabilizations were reported in six patients. Toxicity was typically grade 1 or 2. Grade 3 or 4 neutropenia was reported in five patients and was more common with the daily dose of 800 mg. Grade 3 or 4 non-hematological toxicity was infrequent, and consisted of edema, skin rash and reversible transaminase elevation. Of note, one patient had an intratumoral hemorrhage associated with a documented tumor progression; this adverse event was not considered by the authors to be related to treatment. The authors concluded that imatinib mesylate as a single agent displays promising antitumor activity and a good safety profile in patients with recurrent GBM.

Our report confirms the finding that imatinib is safe for the treatment of patients with AA or GBM that recur after surgery, radiation therapy and chemotherapy with temozolomide. In addition, our experience adds to the mounting evidence that imatinib is active in some patients with high-grade astrocytic tumors. Although serving as proof-of-principle evidence, our data do not allow for firm conclusions regarding the response rate, or the predictors of response in this setting. Targeted therapy is rapidly evolving, and it is becoming increasingly clear that target identification and validation are necessary steps in the development of novel treatment strategies for patients with cancer. At this point in time, targeting the PDGF receptors seems to be a logical strategy, based on the biology of gliomas. Nevertheless, this strategy awaits further validation, and its efficacy requires confirmation. At this point in time, we may speculate that imatinib is more likely to be active for the treatment of patients with secondary GBM – a disease in which the PDGF pathway seems to be more important for gliomagenesis. In line with that hypothesis, our data also suggest that imatinib is more likely to be active among younger patients with high-grade gliomas.

Given these encouraging results, and those from other institutions, we initiated phase II trial to explore the efficacy and safety of high-dose imatinib (800 mg/day) in patients from our population with recurrent AA and GBM.

**CONCLUSIONS**

Imatinib seems to be active in a proportion of patients with high-grade gliomas with PDGF-receptor expression. Moreover, treatment with imatinib is safe for patients who have previously received cerebral radiation therapy and temozolomide.

**REFERENCES**


