Imatinib Mesylate in Chordoma

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BACKGROUND. To the authors' knowledge, no effective medical therapy currently is available for advanced chordoma. Imatinib mesylate is a tyrosine kinase inhibitor targeting platelet-derived growth factor receptor-β (PDGFRB), BCR-ABL, and KIT.
METHODS. Six patients with advanced chordoma were treated with imatinib mesylate at a dose of 800 mg daily. In all patients, the tumor was found to be positive for PDGFRB, and in four patients PDGFRB was shown to be phosphorylated/expressed.
RESULTS. After a treatment period of $\geq$ 1 year, overt tumor liquefaction was evident on computed tomography (CT) scan in the first patient. In previous months, a decrease in contrast enhancement on magnetic resonance imaging (MRI) and a decrease in glucose uptake on positron emission tomography (PET) were detected. Similar signs on MRI and PET were observed in subsequent patients, who had a shorter treatment period. One of these patients initially was removed from therapy and then was readmitted to therapy because of difficulties with regard to tumor response assessment; 1 month after the reinitiation of therapy, an overt decrease in tumor density was visible on CT scan in this patient. In four of five symptomatic patients, a subjective improvement was observed early in the course of treatment. The first patient died after 17 months, with a sizeable, mostly liquefied mass. Another patient died early, apparently of unrelated causes. The remaining patients were on therapy at the time of last follow-up.

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CONCLUSIONS. Imatinib mesylate has been found to have antitumor activity in patients with chordoma. This activity might be mediated by inactivation of PDGFRB. Tumor response manifests through patterns that are similar to those observed in patients with gastrointestinal stromal tumors who respond to molecular-targeted therapy, but evolves more slowly. The benefit to the patient entailed by this pattern of tumor response in chordoma needs to be elucidated, but may be limited in the presence of significant local disease. ***Cancer* 2004;101:2086–97.**

KEYWORDS: chordoma, imatinib mesylate, tyrosine kinase inhibitor, platelet-derived growth factor receptor-β (PDGFRB), response.

Chordomas are very rare tumors, with an incidence of approximately, or slightly lower than, 0.1/100,000/year.[1] They originate from remnants of the notochord.[2] Chordomas arise from the sacrum in approximately 50–60% of cases, from the skull base region in approximately 25–35% of cases, and from the cervical and thoracolumbar vertebrae in approximately 15% of cases (10% from the cervical vertebrae and 5% from the thoracolumbar vertebrae). They are low-grade tumors and display a typical clinical presentation, with lobules and vacuolated (physaliphorous), moderately atypical, neoplastic cells across a myxoid stroma separated by fibrous bands. They generally grow slowly at the primary tumor site. Pain is the cardinal symptom, whereas neurologic deficits are reported to vary according to the size, shape, and location of the lesion(s). Distant metastases can occur, and these also demonstrate a slow pattern of growth. Conversely, "dedifferentiated" chordoma is observed in $< 5\%$ of cases, with features of a high-grade spindle cell sarcoma. Epidemiologically, the median survival has been estimated to be approximately 6 years, with a survival rate of 70% at 5 years, falling to 40% at 10 years.[1] However, after the development of metastases, the median survival was reported to be $<$ 12 months in a series of chordoma patients seen at our institution.[3]

The standard treatment for chordoma is surgery. However, a proportion of chordoma patients (approximately 50–70%) are not cured of their disease and ultimately die. If death is a late event, the patient's quality of life generally is compromised across the relentless natural history of the disease because of the anatomic location of the tumor.[3–6] Radiation therapy is employed either as an adjuvant to subtotal resection, as a definite treatment modality when surgery is clearly unfeasible, or as palliative therapy. Anatomic constraints imply obvious technical problems,[7] and new techniques have been employed in an effort to provide adequate radiation doses while limiting the risk of injury to functionally vital structures.[8–11] Most likely because of their low malignancy grade, chordomas are not reported to be sensitive to chemotherapy. To our knowledge, no drug or regimen has been reported to date to be active in chordomas. Anecdotal reports of tumor responses are available, but the response rate to whatever chemotherapy regimen was used can be assumed to be definitely low.[12,13].

Imatinib mesylate (Gleevec™ [Glivec®], Novartis Pharma AG, Basel, Switzerland) is an inhibitor of some tyrosine kinases, mainly BCR-ABL, KIT, and platelet-derived growth factor receptor-α (PDGFRA) and platelet-derived growth factor receptor-β (PDGFRB). Its inhibition of BCR-ABL and KIT underlies its efficacy in the treatment of chronic myeloid leukemia[14] and gastrointestinal stromal tumors (GIST), respectively.[15–17] This efficacy has been confirmed through large prospective clinical studies.[18–20] Other tumors also have been assessed for imatinib mesylate activity. To our knowledge to date, antitumor activity has been reported in dermatofibrosarcoma protuberans,[21] in which it is mediated through the inhibition of PDGFRB, and aggressive fibromatosis.[22]

In August 2002, at the Istituto Nazionale per lo Studio e la Cura dei Tumori in Milan, Italy, a tumor sample from a patient with an advanced chordoma was tested for molecular targets of potential clinical interest, including PDGFRB. The protein was demonstrated to be expressed and activated. It was speculated that an autocrine loop activating this growth factor receptor could be operating, and, because of the lack of standard therapeutic options, the patient agreed to undergo treatment with imatinib mesylate. Therapy was initiated in August 2002. Subjective improvement was observed, and therapy was maintained. Within some months, both magnetic resonance imaging (MRI) and positron emission tomography (PET) scans suggested some type of antitumor activity. At that stage, an additional five patients were administered therapy, starting from April 2003 to July 2003. This article reports on clinical observations made with regard to these patients.

MATERIALS AND METHODS

In six patients with a histologically confirmed diagnosis of chordoma, the presence of PDGFB was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR), in which RNA extracted from a tumor biopsy was analyzed. All patients were found to demonstrate positive expression of PDGFB. Phosphorylation/expression of PDGFB was demonstrated by immunoprecipitation and Western blot analysis before the beginning of treatment in Patient 1 and retrospectively on pretreatment biopsies taken from Patients 2, 5, and 6. The remaining two patients did not demonstrate phosphorylation/expression, most likely because the amount of tumor material used for total protein extraction was insufficient.

Staging was performed using local MRI and/or computed tomography (CT) scans in all patients, PET scans in all patients but one, and chest CT scans/chest X-rays. During treatment, MRI and/or CT scans were repeated at intervals of 1–3 months. PET scan was repeated at similar intervals in most patients.

All patients received imatinib mesylate on an individual basis, in light of the lack of any potentially effective surgical and/or radiation therapy option, after written informed consent was provided. The patients were aware of the nature of their disease and of the unproven value of the proposed therapy. The drug was provided free of charge by Novartis Pharma AG. All patients received imatinib mesylate at a dose of 800 mg daily. No major adverse effects were observed. Side effects normally associated with imatinib mesylate were reported, but no patient had to discontinue therapy because of toxicity for more than a few weeks.

Case Reports

Patient 1 was diagnosed with a sacral chordoma at the age of 52 years. In 1993, he underwent a posterior sacral amputation (S2-3). A local recurrence developing after 3 years was treated with surgical curettage and radiation therapy (44 + 13 grays [Gy]). After 3 years, a multifocal recurrence to the sacral and gluteal regions was treated with debulking surgery. At that time, bilateral, small metastases of the lung were detected. Further debulking surgery was performed after 1 year. In August 2002, progressive locoregional disease was evident, and the patient began treatment with imatinib mesylate at a dose of 800 mg daily in 2 refracted doses. In the early months after the initiation of therapy, the patient demonstrated some early subjective improvement in terms of the greater softness of the tumor mass palpable in the buttocks and an improvement in pain. At the beginning of the treatment, there was moderate neuropathic and somatic pain, and the patient was being treated with 60 mg of slow-release oral morphine given 3 times daily, plus gabapentin, dexamethasone, and 10 mg of short-release oral morphine as needed. Soon after the initiation of treatment with imatinib mesylate, an increase in the sensation of stabbing and lancinating pain to the gluteal region and the lower limb was reported, necessitating an increase in the dose of gabapentin given. However, after 2 months of therapy, 1) the daily dose of analgesics was not increased, nor were rescue doses used; 2) a decrease in pain was reported, being mild when the patient was sitting and absent when the patient was supine; and 3) the dose of morphine could be decreased from 60 mg 3 times daily to 30 mg twice a day. On MRI, the lesion was judged to be slightly increasing in size in the first months, with some reshaping of the tumor noted in the buttocks, possibly related to its decreased firmness. Between +2 months and +8 months from treatment start, MRI scan demonstrated stable disease (Fig. 1A). However, with intravenous paramagnetic contrast medium (gadolinium-diethylenetriamine pentaacetic acid [Gd-DTPA]), the contrast enhancement (Fig. 1B) was found to be substantially lower. This major decrease in contrast enhancement was found to be correlated with a decrease in glucose uptake on the PET scan between +2 months and +6 months (Fig. 2). Between +8 months and +14 months, the tumor aspect on T1-weighted, contrast-enhanced images was found to be the same, with high-signal intensity noted on T2-weighted images. At this time, CT scan demonstrated distinct signs of tumor liquefaction (Fig. 3A) in a substantial portion of the tumor volume (Fig. 3B). Clinically, this paved the way for a spontaneous spillage from the buttocks of a dense fluid with overt tumor debris. Figure 4 shows the histologic aspect of the spillage, which was consistent with marked tumor regressive changes along with apoptotic figures. Biochemical analyses were performed on the tumor material, and a nonphosphorylated, inactive PDGFRB was detected (Fig. 5). In the interim, lung metastases remained unchanged, as did glucose uptake on the PET scan. Pain was controlled with a daily dose of 60 mg of morphine. Conversely, tumor liquefaction required special local care and was found to impair the daily life of the patient to a significant extent. The patient's general condition worsened progressively, apparently in connection with the persistent, although mostly liquefied, tumor mass, with episodes of septic fever reported. Death occurred 17 months from the initiation of treatment.

Patient 2 was diagnosed with a sacral chordoma at the age of 25 years. He underwent curettage of the sacrococcigeal lesion. Because of evident disease, the patient underwent a limited excision in January 2001,

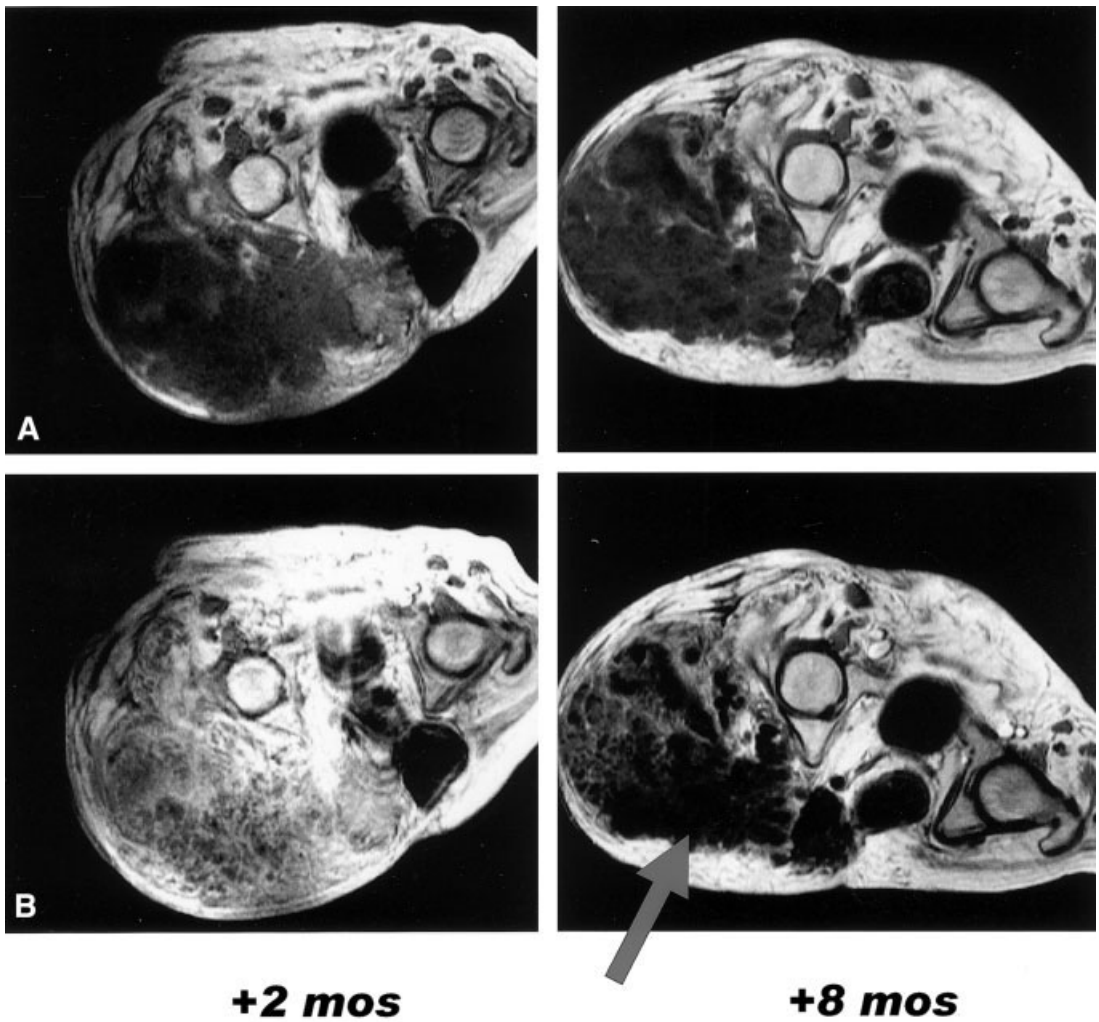

FIGURE 1. Axial, T1-weighted magnetic resonance imaging scan in Patient 1. At 8 months, there was a minor decrease noted with regard to tumor size, but the main feature observed was (B) decreased contrast enhancement (arrow).

followed by a sacral amputation (S3) 1 month later. Radiation therapy followed (at a dose of 64 Gy). In October 2002, a recurrence to the gluteal region occurred, which was treated with a wide excision. In April 2003, disease recurrence was evident in both gluteal regions. Imatinib mesylate at a dose of 800 mg daily was initiated in April 2003. One month after the initiation of therapy, an increase in the tumor volume was apparent. Therapy was maintained for 4 months and then withdrawn when a further increase in tumor volume was evident and the patient reported an increase in pain. Indeed, a PET scan detected some decrease in the glucose uptake at +1 month and +3 months. Therapy was switched to a high-dose prolonged infusion of ifosfamide (14 g/m^2 over 14 days through an external infusion pump), but further disease progression was detected. At this time, a clearcut contrast enhancement was noted (Fig. 6) and it was appreciated retrospectively that it had decreased while the patient was receiving imatinib mesylate therapy at +4 months, paralleling a high signal intensity on T2-weighted images (i.e., the same pattern recorded in Patient 1 after 8 months). It then was decided to readminister imatinib mesylate. At this stage, lung metastases became visible. One month after therapy was readministered, the significant locoregional lesion increased in size, whereas tumor density as observed on CT scan decreased by roughly 50% (Fig. 7). Subjectively, the mass appeared to have increased overtly in size, but was less firm. Wide skin ulcers became present, and necrotic debris was evident throughout these ulcers. At the time of last follow-up, these ulcers required continuous local care, although some symptoms had improved (stipsis and, in part, pain) and the patient was able to remain in the sitting position, whereas he was completely bedridden

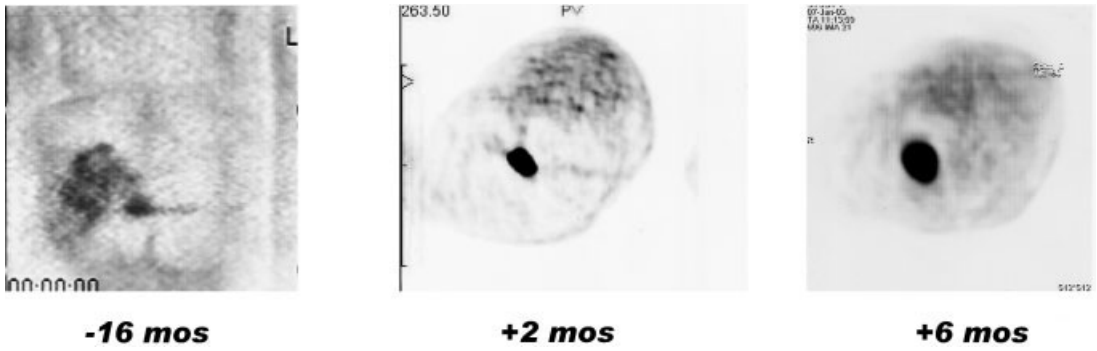

FIGURE 2. A positron emission tomography (PET) scan in Patient 1. At 6 months, there was some decrease reported in the glucose uptake of the sacral/gluteal lesion noted on the PET scan. Because of the lack of a baseline assessment, comparison was made with a pretreatment evaluation dating back several months.

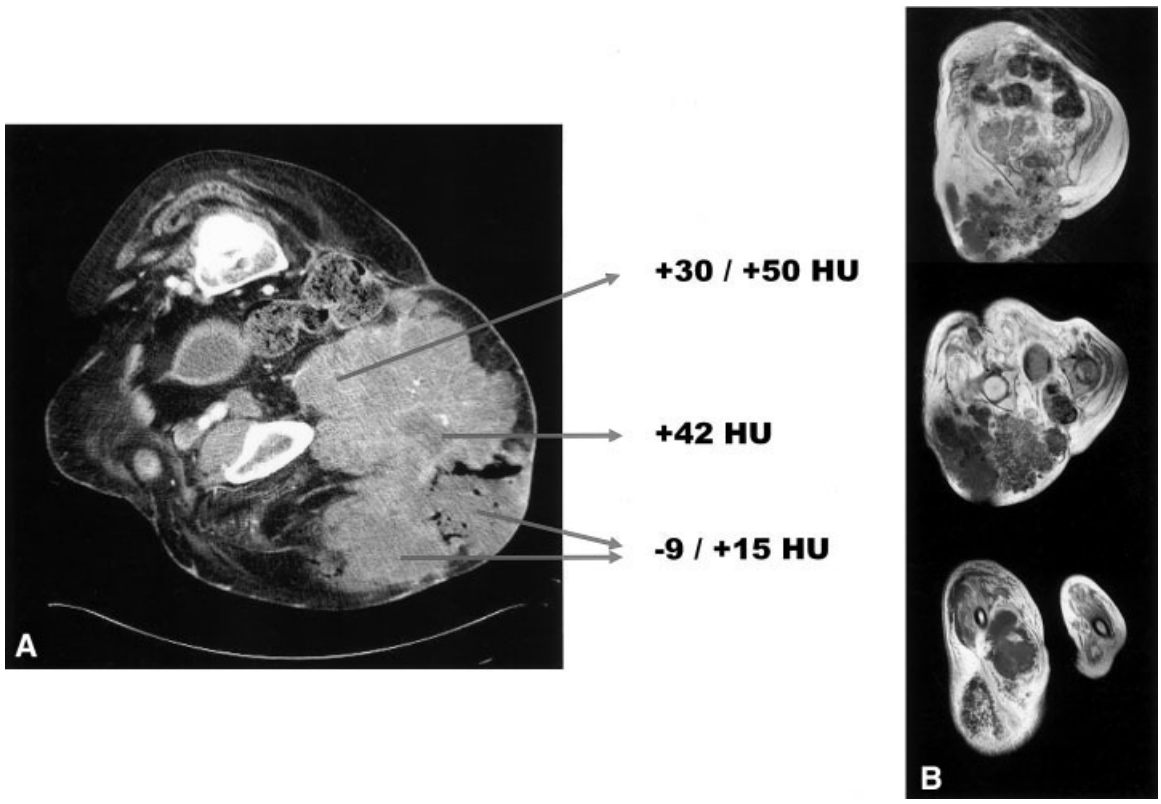

FIGURE 3. Patient 1. (A) Areas of low density (expressed in Houndsfield units [HU]) were visible throughout the lesion on the CT scan, with (B) low contrast enhancement noted on T1-weighted magnetic resonance imaging from most cranial to most caudal sections.

after the readministration of imatinib mesylate. Therapy was continuing at the time of last follow-up.

Patient 3 was diagnosed with a chordoma of the clivus in 1998 at the age of 58 years. He underwent embolization and partial excision of the tumor, which had a sphenoideal, ethmoidal, and nasopharyngeal extent. Because of disease progression, the patient underwent several surgical debulking excisions in January 2000, September 2000, January 2002, May 2002, and October 2002. In April 2001, proton/photon beam radiation therapy was administered to the residual tumor. Treatment with imatinib mesylate was initiated at a dose of 800 mg daily from May 2003 onward. The patient died 3 months from the initiation of therapy, apparently of unrelated causes. MRI scan at +2 months illustrated a decrease in contrast enhancement on T1-weighted images, although with some slight increase in the tumor volume and some signs of

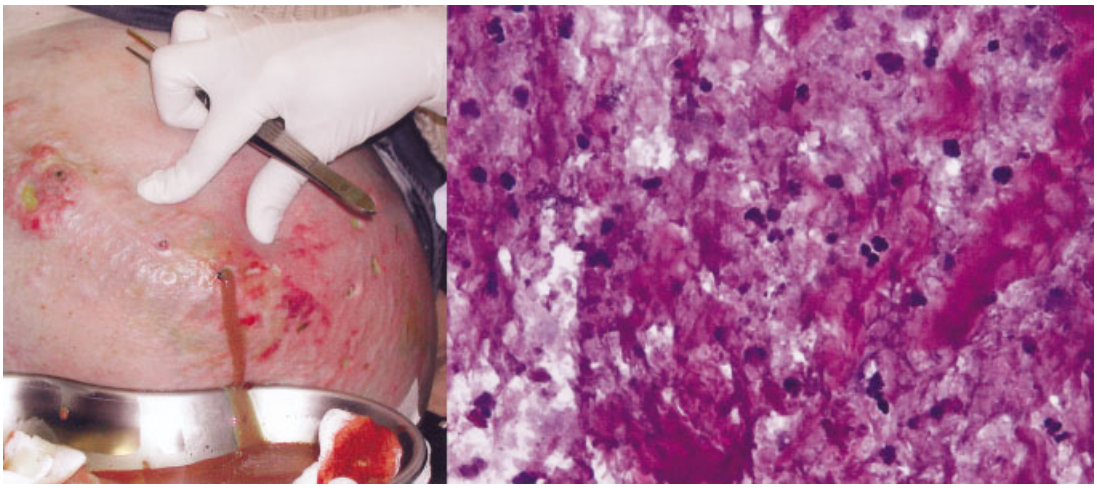

FIGURE 4. Patient 1. Spontaneous spillage from the lesion of semifluid material occurred, with a pathologic aspect consistent with markedly apoptotic regressive changes.

internal bleeding were noted at +3 months, all of which were suggestive of an initial response. Some initial decrease in symptoms resulting from local compression (e.g., improvement in swallowing) were reported by the patient.

Patient 4 was diagnosed with a sacral chordoma in 1995 when she was age 41 years. Sacral amputation (S1-2) was performed with suboptimal surgical margins, followed by radiation therapy (at a dose of 60 Gy). Because of a pelvic disease recurrence after 5 years, a surgical excision was performed in 2000. In June 2002, pelvic nodules were surgically excised. In May 2003, because of the presence of evident pelvic disease, treatment with imatinib mesylate was initiated at a dose of 800 mg daily. Although there appeared to be a progressive, slight increase in the tumor volume within the first 5 months after the initiation of treatment, the patient presented with a consistent decrease in contrast enhancement (Fig. 8). PET scan demonstrated a minor decrease in glucose uptake. At the time of last follow-up, the patient reported that her pain was well controlled through a dose of methadone which had not been increased since the initiation of treatment, whereas it needed to be continuously increased earlier in the patient's treatment.

Patient 5 was diagnosed with a sacral chordoma in 1993 at the age of 48 years. A pelvic mass was surgically excised, followed by radiation therapy (at a dose of 40 Gy). After 6 years, proton beam radiation therapy was given for a local recurrence (70 cobalt Gy equivalent), with a partial response achieved. Liver metastases were evident in 2003 and were confirmed histologically through a biopsy, along with local disease progression. Imatinib mesylate at a dose of 800 mg daily was initiated beginning in July 2003. At the time of last follow-up, the patient was unevaluable to the sacrum, whereas the liver lesions demonstrated some initial decrease in size on the CT scan at 3 months after the beginning of therapy (Fig. 9). PET scan demonstrated some decrease in glucose uptake, especially with regard to the maximum standard uptake (SUVmax) values (from 6.7 g/mL to 5.5 g/mL). At the time of last follow-up, the patient remained asymptomatic and was receiving therapy.

Patient 6 underwent debulking surgery in April 2003 at the age of 73 years for a chordoma that involved the sacrum and the left iliac wing extensively, as well as the surrounding soft tissues. Treatment with imatinib mesylate was initiated in July 2003 because of the presence of involvement of both gluteal regions. The patient demonstrated some minor increase in tumor volume after the initiation of therapy; however, the lesions demonstrated less contrast enhancement from +2 months onward, with high signal intensity noted on T2-weighted images. This pattern of tumor response continued to be apparent until the last examination performed at 6 months (Fig. 10). PET scan showed a decrease in glucose uptake after 2 months, and the glucose uptake continued to decrease both with regard to the median and maximum SUV through the last examination performed at 8 months. At the time of last follow-up, the patient reported that the pain was well controlled with the same analgesic therapy that was administered on starting imatinib mesylate, whereas the sacral mass appeared to be less firm, although it had appeared to increase in size. However, at the time of last follow-up, the patient was able to maintain a sitting position, unlike before treatment was initiated.

FIGURE 5. Patient 1. Expression and phosphorylation status of platelet-derived growth factor receptor-β (PDGFRB) prior to and after treatment. (A) Expression and phosphorylation status of PDGFRB prior to treatment ("Patient 1" compared with a negative, "C-" and a positive control "C+"). *For each lane, 800 μg of total protein extracts were immunoprecipitated with αPDGFRB antibody, run on gel, and blotted with the indicated antibodies.* (B) Reverse transcriptase-polymerase chain reaction for PDGFB (ligand). A band corresponding to the ligand was detected in this patient, as it was in all patients in the current series. *MWM: standard molecular weight marker. One microgram of RNA was retrotranscribed to cDNA and amplified with primers specific for PDGFB* (C) Expression of PDGFRB in the tumor before and after therapy. PDGFRB was detected only before therapy. *Equal amounts of total proteins (80 μg) were loaded onto a gel. The membrane was incubated with PDGFRB antibody.*

DISCUSSION

Of six patients with advanced chordoma and biomolecular signs of involvement of PDGFRB, one demonstrated overt liquefaction of a substantial portion of his primary tumor after several months of therapy, during which time indirect signs of tumor response could be observed radiologically. A striking decrease in tumor density also was observed in the second patient after therapy was readministered after a temporary interruption because of misinterpretation of the same radiologic signs. These radiographic findings have been consistently observed in the other patients after shorter treatment intervals. Such findings mainly were observed in terms of a decrease in contrast enhancement on MRI and glucose uptake on PET scans. Some early subjective benefit was observed in the majority of patients, although, after several months, tumor liquefaction of a significant tumor mass did not result in a benefit for the first patient, who ultimately died. Likewise, the quality of life of the second patient was greatly affected by his mostly liquefied tumor mass, although at the time of last follow-up the patient appeared to be slowly improving. In most patients, tumor response evolved slowly, in a way that appears very similar to patients with GIST responding to molecular-targeted therapy. Table 1 summarizes the antitumor effects described above.

These chordoma patients were treated with imatinib mesylate on the assumption that PDGFRB might be implicated in tumor growth. In fact, we observed that PDGFRB was phosphorylated/expressed in the first patient and PDGFB was present in all the remaining patients. Retrospectively, phosphorylation/expression could be detected in the three other patients in whom there was a sufficient amount of frozen tissue for immunoprecipitation/Western blot analysis. This is not tantamount to a formal demonstration of the involvement of PDGFRB in the growth process of chordomas. However, the results of the current study are suggestive. At the time of last follow-up, all 18 chordoma patients tested at our institution were found to be positive for either the presence of PDGFB or expression/phosphorylation of PDGFRB (data not shown). Furthermore, by comparing samples obtained before and after treatment in Patient 1, PDGFRB inactivation after therapy could be demonstrated biochemically. Histologically, this finding was accompanied by the presence of distinctly apoptotic cells. In brief, these findings strongly suggest that further investigation of the role of PDGFRB in chordomas is necessary. However, other mechanisms of action of imatinib mesylate cannot be excluded at the current time.

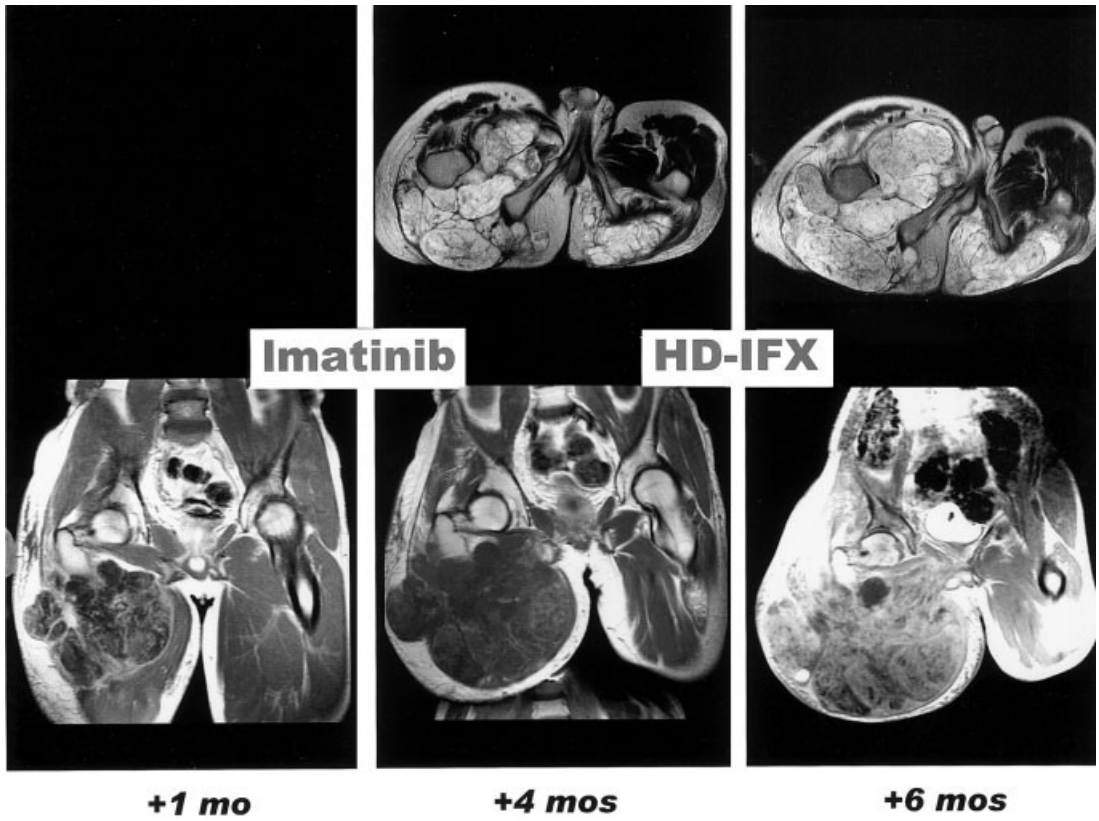

FIGURE 6. Magnetic resonance imaging (MRI) in Patient 2. Despite the increase in size, lower contrast enhancement was evident after treatment with imatinib on T1-weighted MRI. Contrast enhancement was again visible after the disease progressed after chemotherapy. HD-IFX: high-dose ifosfamide.

We observed an early subjective improvement in the first patient, and therefore treatment with imatinib mesylate was maintained. In fact, tumor size did not appear to change substantially over several months. However, in this first patient, contrast enhancement as noted on MRI scan and glucose uptake as noted on PET scan were found to decrease consistently in a matter of months. A similar evolution was observed in subsequent patients, although often in the presence of some initial increase in tumor volume. These findings would hardly be explicable in the absence of some kind of antitumor activity of imatinib mesylate. Indeed, PET scanning is the earliest and most reliable indicator of tumor response in GIST patients treated with the same agent (more precisely, it may be viewed as an early "predictor" of the response of GISTs to imatinib mesylate). Most important, those radiologic signs were found to precede overt tumor liquefaction in the first two patients reported herein. We believe that this is enough evidence to suggest that imatinib mesylate has some type of antitumor activity in chordoma and that, possibly, this activity might be of major significance. Of course, clinical studies are needed to quantify the response rate and evaluate the medium/long-term impact of treatment in terms of survival and quality of life.

After the experience of molecular-targeted therapy in patients with GIST, it has now become well accepted by the medical oncology community that the tumor response manifests differently from what we ordinarily observe with cytotoxic agents in solid neoplasms (as well as, paradigmatically, in lymphomas). In GISTs, one of the most striking clinical findings has been that the tumor response to molecular-targeted therapy with imatinib is often manifested by: 1) early signs of subjective improvement and a decrease in glucose uptake on the PET scan;[23] 2) midterm signs of a decrease in tumor density on the CT scan and a change in the signal intensity on the MRI scan even without a noticeable impact on tumor size, which indeed also may increase;[24,25] and 3) delayed signs of a decrease in the size of the tumor and/or tumor stabilization with altered tumor density. Histologically, signs of response are cellular depletion with varying degrees of an apoptotic tumor cell population and a stromal myxoid degeneration[17]. This most likely reflects the mechanisms of action of molecular-targeted therapy, with an initial "functional" effect on

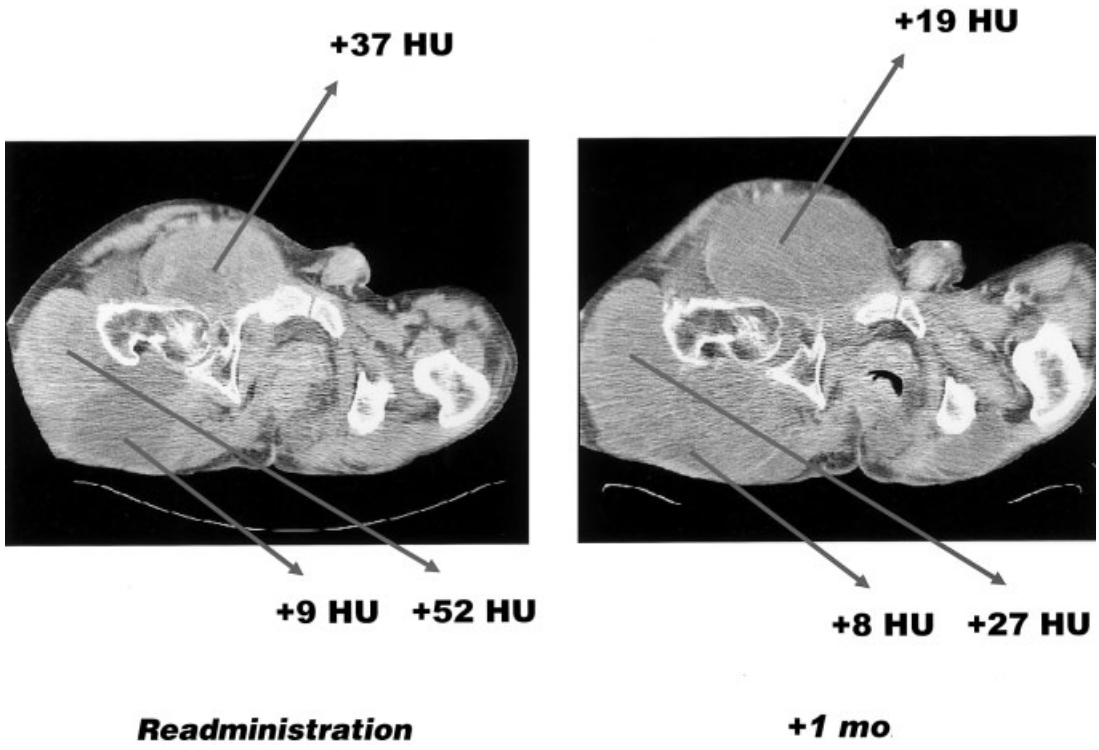

FIGURE 7. Computed tomography (CT) scan in Patient 2. One month after therapy was reinitiated, the lesion increased in size and could not be examined in its entirety using CT scan or magnetic resonance imaging. However, the portion that was assessable through the CT scan demonstrated an obvious decrease in the tumor density (as expressed in Houndsfield units [HU]) compared with 1 month previously.

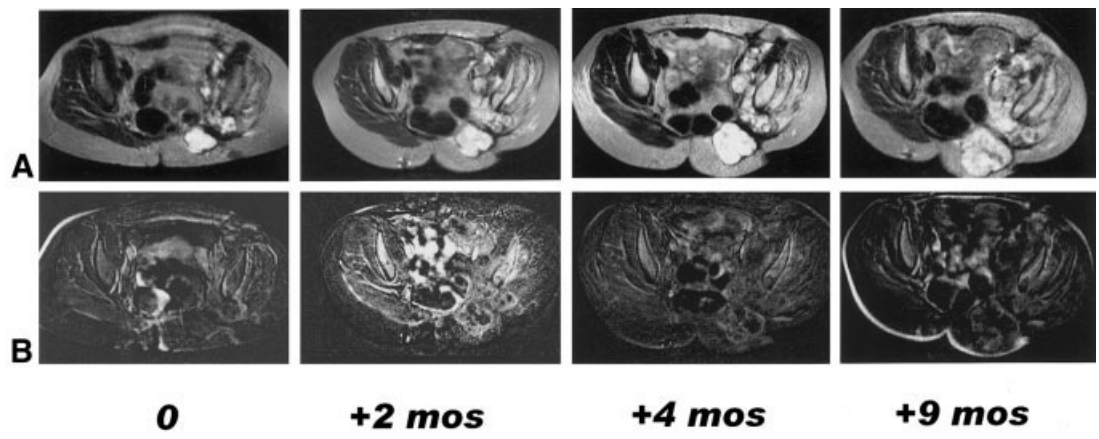

FIGURE 8. Magnetic resonance imaging in Patient 4. Some increase in size was visible in the first months of therapy, but it was accompanied by a higher signal on the T2-weighted images and a decreased contrast enhancement on T1-weighted images with contrast subtraction.

tumor metabolism, followed by an effect on the characteristics of the tumor tissue and eventually some more conventional impact on tumor size. This time evolution of the tumor response also occurred in these patients with chordoma. However, the size of the residual masses did not appear to regress significantly, even after several months, so that major clinical complications were encountered in the two patients who began treatment with the largest tumor lesions. This might be explained in at least two ways. First, the histological hallmark of chordomas is acellular myxoid material and a varying amount of a heterogeneous cellular component comprised of syncythial cell cords and/or strands arranged into lobules. Therefore, a response with regard to tumor size may be slower and/or less pronounced in patients with chordomas

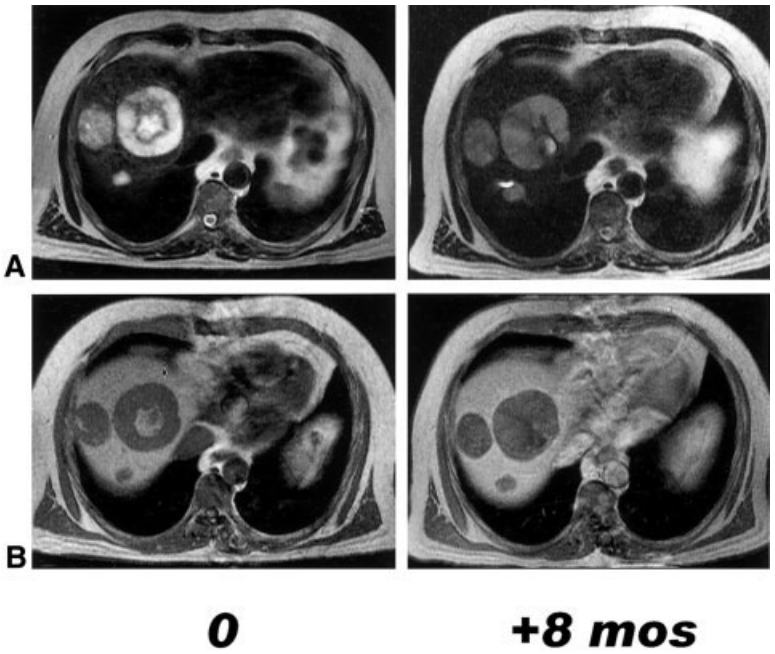

FIGURE 9. Magnetic resonance imaging in Patient 5. Lower contrast enhancement and a slight decrease in the size of markedly nonhomogeneous liver metastases was evident after therapy (Panel A: T2-weighted image; Panel B: T1-weighted, image).

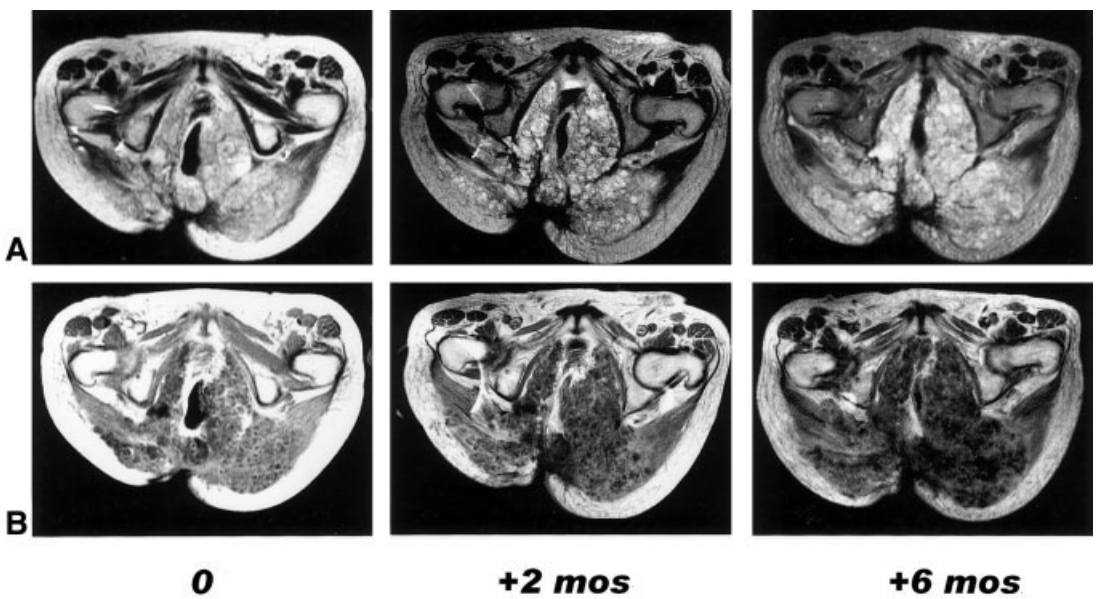

FIGURE 10. Magnetic resonance imaging in Patient 6. Over a period of 2–6 months, despite some initial increase in size, the lesions demonstrated a higher signal on T2-weighted images (A) and a decrease in contrast enhancement on T1-weighted images (B).

compared with those with the more cellular GIST, and only very indirect radiologic signs may herald a late obvious impact on the tumor. Second, the molecular target of therapy might influence patterns of response. In this sense, PDGFRB and related pathway(s) may act as a competence factor, as opposed to other factors related more directly to cell growth. However, our impression was that similarities with GIST prevailed, both clinically and radiologically, although on a different time scale. In addition, in the first patient reported herein, although after a long treatment period, marked cellular regressive changes with a high rate of apoptotic figures were evident histologically in the fluid that spilled out of the tumor site, a finding that is consistent with that noted in GIST patients.

From the clinical point of view, these patterns of response may have two implications. First, signs of tumor response to molecularly-targeted agents have

TABLE 1
Summary of the Antitumor Effect

Effect	No. of patients	No. of evaluable patients	Timing	Assessment
Effect on tumor tissue	6	6	Early/mid-term/late (wks to mos)	MRI (contrast enhancement/T2-weighted); PET; CT (contrast/density)
Effect on tumor metabolism	5	5	Early (wks)	PET
Effect on symptoms	4	5	Early (wks)	Subjective

MRI: magnetic resonance imaging; PET: positron emission tomography; CT: computed tomography.

proven to be more difficult to detect than expected. Second, the fact that the response may be slow, and also may be preceded by some initial increase in the size of the lesions or may not result in a substantial decrease in tumor volume, could result in clinical complications. For example, a spinal chordoma may compress the spinal cord by enlarging in the early phases of therapy. More important, as observed in the first two cases reported in the current series, even major tumor liquefaction, if occurring within large lesions, may give rise to adverse clinical consequences and ultimately be detrimental. Indeed, this finding occasionally also is observed in patients with GIST who have enormous tumors. The persistence of these masses, although not vital, occasionally may be of little help to the patient, and local complications may be of major significance. Thus, the clinical utilization of molecularly-targeted therapy always should consider both its peculiar pattern of response and the clinical presentation in the specific patient.

On the basis of these preliminary results, a formal Phase II assessment of imatinib mesylate in patients with chordoma is currently underway. This will allow for the verification of how frequently, to which degree, and in which way molecularly-targeted therapy is active in this disease entity. Indeed, in light of the lack of conventional medical therapies for such a rare disease, there is a clinical need to be urgently met and, most likely, even what has been reported in the current small series of cases will prompt individualized clinical decisions in selected patients with advanced chordoma. However, it would be of vital importance to prospectively register all those patients who would be treated with imatinib mesylate. Furthermore, patterns of tumor response as discussed herein need to be considered, so that tumor responses are not missed. Most important, clinicians must be aware of the fact that even major tumor liquefaction within a large tumor mass might not necessarily translate into substantial medium-term benefits for patients with very advanced disease. It is likely that this therapy should be utilized at an earlier stage of disease. In future clinical investigations, it might be wise, especially in the case of so rare a neoplasm, to evaluate the antitumor activity of imatinib mesylate within multidisciplinary approaches, including surgery and/or radiation therapy.

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