Response to imatinib plus sirolimus in advanced chordoma

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Background: Imatinib (IM) is active in advanced chordoma. The evidence of upstream and/or downstream mammalian target of rapamycin (mTOR) pathway activation prompted us to combine an mTOR inhibitor, sirolimus, to IM in IM-resistant advanced chordoma.

Patients and methods: Since July 2007, 10 progressive advanced chordoma patients with secondary resistance to IM, and biochemical and/or immunohistochemical evidence of upstream and/or downstream mTOR effector activation, started IM (400 mg/day) plus sirolimus (2 mg/day) on a named basis.

Results: The mean treatment duration was 9 months. Of nine patients assessable for response, at 3 months, we had one RECIST partial response (PR), seven stable disease (SD) and one progressive disease (PD). According to Choi criteria applied even to magnetic resonance imaging, we had seven PR (‡10% decrease in size in four cases), one SD and one PD. Seven patients had a positron emission tomography response. The clinical benefit [RECIST complete response + PR + SD ‡6 months] was 89%. Pretreatment mTOR effectors analysis carried out in nine cases was positive in all patients (AKT activation in six patients, S6Sp6 expression/activation in seven). Post-treatment biopsy in one responsive patient confirmed S6 switch off.

Conclusion: In addition to PDGFRB, mTOR pathway can be activated in chordomas and the combination of IM plus rapalogs may be effective in IM-resistant chordomas.

Key words: chordoma, imatinib, mTOR, rapamycin, sarcoma, sirolimus

Introduction

Chordomas are very rare tumors of bone (incidence 0.1/100 000 per year) [1]. They occur in the axial skeleton, most frequently in the sacrococcygeal region, while the skull base is more often involved in young patients. They are in general low-grade malignancies with epithelial/mesenchymal differentiation and, usually, the clinical course of the disease is slow and mainly local. An aggressive ‘dedifferentiated’ high-grade variety may occur in <5% of patients [2]. Chordomas do have even a metastatic potential to the lungs, bone, liver and soft tissue, but locoregional disease is generally the main problem. In fact, local recurrences affect >50% of the patients [3–8]. Most of the patients who relapse locally cannot be cured and have an ultimately poor prognosis, in spite of a long history. Both surgery and radiation therapy can be used as salvage therapy, but in case of failure medical treatments are needed. Chemotherapy has long been known to be inactive in chordoma. Reports of tumor responses to regimens including anthracyclines, cisplatin and alkylating agents have been only anecdotal [9], while a phase II study on topoisomerase I inhibitor, 9-nitro-camptothecine, has shown one objective response over 15 chordoma treated patients with a median 6-month progression-free rate of 33% [10]. Among molecular target therapy, imatinib mesylate (IM) has been shown to be active, inhibiting PDGFRB activation. Secondary progression to imatinib after response can occur [11, 12]. Anecdotal report describes a response to epidermal growth factor receptor (EGFR) inhibitor, cetuximab and gefitinib [13]. We reported that the addition of low-dose cisplatin to imatinib in patients with secondary progression on imatinib alone can restore a response, indicating a possible synergism between the two drugs [14].

The mammalian target of rapamycin (mTOR) pathway deregulation is involved in tumor growth in a number of tumors and it is known that the disruption of mTOR signaling suppresses the cell cycle progression and angiogenesis [15]. Drugs able to inhibit mTOR have been proved to be active in renal carcinoma [16] and studies are now open to evaluate their activity in other tumors, including sarcoma [17]. We described a switch on of mTOR signaling, sustained by upstream
Table 1. Results: treatment duration, side effects and response; pre and post-treatment mTOR effectors molecular analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of treatment (stopped/ongoing)</th>
<th>Hematologic toxicity</th>
<th>Non-hematologic toxicity</th>
<th>Assessable for response</th>
<th>Symptoms improvement</th>
<th>Best response: RECIST (modality)</th>
<th>Best response: Choi’s criteria (modality)</th>
<th>PET response</th>
<th>Pretreatment pAKT</th>
<th>Pretreatment S6/pS6 IHC</th>
<th>Post-treatment S6/pS6 WB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 (ongoing)</td>
<td>Neutropenia G3, leucopenia G2, piastrinopenia G1</td>
<td>Mucositis G2, diarrhea G2</td>
<td>Yes</td>
<td>Yes</td>
<td>SD (MRI)</td>
<td>PR (MRI)</td>
<td>Yes</td>
<td>Positive</td>
<td>Positive/positive</td>
<td>Not assessed</td>
</tr>
<tr>
<td>2</td>
<td>15 (ongoing)</td>
<td>Anemia G2</td>
<td>Infection (local abscess)</td>
<td>Yes</td>
<td>Yes</td>
<td>SD (CT/MRI)</td>
<td>PR (CT/MRI)</td>
<td>Yes</td>
<td>Positive</td>
<td>Positive/positive</td>
<td>Not assessed</td>
</tr>
<tr>
<td>3</td>
<td>15 (stopped)</td>
<td>Anemia G1, piastrinopenia G2, leucopenia G1, neutropenia G3, lymphopenia G1</td>
<td>Lower limbs edema G2</td>
<td>Yes</td>
<td>Yes</td>
<td>PR (CT)</td>
<td>Not assessed</td>
<td>Yes</td>
<td>Positive</td>
<td>Positive/positive</td>
<td>Positive/positive</td>
</tr>
<tr>
<td>4</td>
<td>12 (ongoing)</td>
<td>Leucopenia G1, neutropenia G1</td>
<td>Mucositis G2 infection (H labialis)</td>
<td>Yes</td>
<td>Yes</td>
<td>SD (CT/MRI)</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Positive/positive</td>
<td>Not assessed</td>
<td></td>
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<tr>
<td>5</td>
<td>9 (stopped)</td>
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<td>Infections (pneumonia, recurrent urinary tract infections)</td>
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<td>Worsening</td>
<td>SD (CT/MRI)</td>
<td>SD (CT/MRI)</td>
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<td>Not assessed</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8 (stopped)</td>
<td>Anemia G2, leucopenia G2, neutropenia G2</td>
<td>Infection (Herpes zoster)</td>
<td>Yes</td>
<td>Yes</td>
<td>SD (CT)</td>
<td>PR (CT)</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Positive/positive</td>
<td>Not assessed</td>
</tr>
<tr>
<td>7</td>
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<td>Not applicable</td>
<td>No</td>
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<td>Not evaluable</td>
<td>PR (CT)</td>
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<td>Not assessed</td>
<td>Positive/positive</td>
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</tr>
<tr>
<td>8</td>
<td>9 (ongoing)</td>
<td>Anemia G1</td>
<td>Mucositis G2, diarrhea G2, infection (Herpes labialis)</td>
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<td>Not evaluable</td>
<td>Not evaluable</td>
<td>PR (CT)</td>
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<td>Not assessed</td>
<td>Positive/positive</td>
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<td>4 (ongoing)</td>
<td>Anemia G1</td>
<td>None</td>
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<td>SD (CT/MRI)</td>
<td>PR (CT/MRI)</td>
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<td>Yes</td>
<td>Worsening</td>
<td>SD (CT/MRI)</td>
<td>PD (CT/MRI)</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Positive/positive</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

PET, positron emission tomography; IHC, immunohistochemistry; WB, western blotting; SD, stable disease; MRI, magnetic resonance imaging; PR, partial response; CT, computed tomography; PD, progressive disease.
activated RTKs in a number of naive chordoma patients (submitted for publication). These findings along with the evidence of some mTOR surrogate effectors in few cases of imatinib-resistant chordoma prompted us to combine imatinib with sirolimus (rapamycin, Rapamune®), an inhibitor of mTOR kinase that acts binding an intracellular protein, FKBP-12, thus forming a complex that blocks mTOR signaling [18].

**patients and methods**

From July 2007 to October 2008, 10 patients with advanced chordoma progressive to imatinib either in monotherapy or in combination with cisplatin were treated with imatinib plus sirolimus at Istituto Nazionale Tumori, Milan, Italy, within a compassionate use program. The primary aim was to explore if the combination of sirolimus plus imatinib had any activity in chordoma.

**eligibility**

All patients treated in this series had to have a diagnosis of locally advanced or metastatic unresectable chordoma. They had to be proven resistant to imatinib in monotherapy, with evidence of progressive disease (PD) during the previous 3 months and measurable according to the RECIST [19]. A performance status (PS; Eastern Cooperative Oncology Group) of three or less and an adequate bone marrow and organ function were also requested.

Histological diagnosis of chordoma was reviewed and confirmed in all cases. PDGFB/PDGFRB (biomolecular and/or immunohistochemical) assessment was carried out as previously described [11]. The status of AKT and S6, upstream and downstream mTOR effectors, respectively, was analyzed by a direct western blot, loading 20 μg/lane of total protein extract and using the following antibodies: anti-pAKT (#4058S ser473; Cell Signaling), anti-AKT (#9272; Cell Signaling), anti-pS6 (#2215L ser240/244; Cell Signaling), anti-S6 (#2217; Cell Signaling) and anti-actin (A2066; Sigma, Sant Louis, MO). Immunohistochemistry for S6 and pS6 was carried out using the same Cell Signaling antibodies on the tumor formalin-fixed specimens obtained before sirolimus treatment. Post-treatment biopsy was taken in one patient 8 weeks after starting sirolimus.

Patient’s written informed consent to a nonconventional medical treatment, selected in the lack of alternative therapies known to be effective in the disease, was required, and all patients were aware that there was not any previously reported proof of antitumor activity and efficacy of imatinib in combination with sirolimus.

**treatment**

Patients were treated with 400 mg of imatinib once daily plus daily oral sirolimus. Sirolimus was started in all cases at the dose of 2 mg/day, to be taken once a day always at the same time, either with low-fat food or without food. The dose was individually adjusted according to the blood level of the drug in order to keep it in the range between 15 and 20 ng/ml.

**Figure 1.** RECIST partial response on computed tomography scan after 3 months [(A) baseline, (C) +3 months] confirmed by positron emission tomography [(B) baseline, (D) +3 months]; S6 inactivation (absence of phosphorylation) was confirmed on western blotting analysis performed on biopsy taken after 8 weeks (red arrow).
Patients had to avoid drugs metabolized by the cytochrome P-450 (CYP) 3A4, with the exception of steroids that were allowed when strictly necessary. Grapefruit juice also had to be avoided.

Treatment was continued until progression or toxicity. Treatment was withheld for hematologic grade ≥3 adverse events and for non-hematologic grade ≥2 adverse events (defined according to the National Cancer Institute—Common Toxicity Criteria, version 3.0) and restarted after recovery to grade ≤2 in case of hematologic or grade ≤1 in case of non-hematologic adverse event.

evaluation
At baseline, all patients were evaluated with a complete history and physical examination, a complete blood count and serum chemistry (comprehensive of absolute neutrophil count, platelet, hemoglobin, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, cholesterol and triglycerides) and full cardiologic assessment. Adverse events, serum chemical analyses and blood count were monitored biweekly for the first 3 months, than monthly but in case of problems. Required imaging studies before treatment included a whole body computed tomography (CT) scan and a CT scan and magnetic resonance imaging (MRI) of the site/sites of disease; baseline positron emission tomography (PET) scan was carried out in all cases but the one with skull base chordoma. Scanning was repeated after 46 weeks from treatment start than every 3 months.

efficacy assessment
Response to treatment was assessed with the use of both RECIST and Choi’s criteria, as recently defined for gastrointestinal stromal cancer (GIST) [20] and adapted even to MRI [21], and PET response.

In particular, Choi’s criteria are based on changes in tumor size and density following contrast administration on CT scan. We applied Choi’s criteria even to MRI, assuming that changes in contrast enhancement on subtracted contrast-enhanced T1-weighted sequences parallel changes in density on CT, both being markers of tumor vascularization. Therefore, according to Choi’s criteria, a radiological partial response (PR) was defined by the presence of a ≥10% decrease in tumor size or a ≥15% decrease in tumor density/contrast enhancement on CT/MRI, while progression was qualified in case of new lesion or in case of ≥10% increase in tumor maximal diameter without any criteria for PR by tumor density/contrast enhancement or ≥15% increase in tumor density/contrast enhancement without any criteria for PR by tumor size. Finally, a PET PR was defined as a ≥25% decrease in maximum standardized uptake (SUVmax) according to the currently available European Organization for Research and Treatment of Cancer 1999 tumor response criteria [22].

role of the funding source
Novartis Pharma provided imatinib on a case-by-case basis and was informed of the results. The corresponding author had the final responsibility for the decision to submit the paper for publication and wrote the manuscript in cooperation with all the other authors. The company played no role in writing or revising the manuscript.

results
From July 2007 to October 2008, 10 patients with advanced chordoma resistant to imatinib in monotherapy were treated with imatinib plus sirolimus. Five patients are still on treatment. One stopped his treatment very early due to worsening of his general condition and he is not assessable for response. He died 1 month later. The others stopped their treatment after 1, 8, 9 and 15 months, respectively, due to the

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Site of primary tumor</th>
<th>Disease extension</th>
<th>Expression</th>
<th>Pretreatment biopsy</th>
<th>Chemotherapy</th>
<th>Pretreatment status</th>
<th>Site of biopsy</th>
<th>Previous surgery/chemotherapy</th>
<th>Pretreatment biopsy</th>
<th>Chemotherapy</th>
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<tr>
<td>59</td>
<td>Female</td>
<td>0</td>
<td>LR</td>
<td>PDGFβB (IHC)</td>
<td>LR + M (lung, liver)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes/yes/no</td>
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<td>47</td>
<td>Female</td>
<td>0</td>
<td>LR</td>
<td>PDGFβB (IHC)</td>
<td>LR + M (lung, liver)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/yes/no</td>
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<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/yes/no</td>
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<tr>
<td>18</td>
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<td>0</td>
<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
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<td>Yes</td>
<td>No</td>
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<tr>
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<td>2</td>
<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>3</td>
<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes/yes/no</td>
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<td>78</td>
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<td>2</td>
<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
<td>No</td>
<td>Yes</td>
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<td>Yes/yes/no</td>
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<tr>
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<td>Male</td>
<td>6</td>
<td>LR</td>
<td>PDGFβB (RT PCR)</td>
<td>LR + M (lung, liver)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/yes/no</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PDGFβB, platelet-derived growth factor βB; PDGFβF, platelet-derived growth factor βF; IHC, immunohistochemistry; RT PCR, real-time PCR.
evidence of progression. Nine are assessable for tumor response. Results are summarized in Table 1.

**pathology and biology**

At progression on imatinib, before starting treatment with imatinib and sirolimus, fresh and/or formalin-fixed material for the assessment of AKT and/or S6 status was available in nine cases. In all cases, there was evidence of the activation of AKT and/or S6/S6K.

In patient 3, the status of S6 assessed after 8 weeks of treatment showed that it was no more phosphorylated as it was before treatment (Figure 1).

**patients**

Main patient characteristics are listed in Table 2 (mean age 56 years, range 18-78; female/male: 4/6; site: nine sacrum, one skull base; locoregional/metastatic: 4/6, with involvement of the lung (six), liver (four) and soft tissue (three)). The PS was two or more in 50% of them (0 in three, 1 in two, 2 in three and 3 in two). All patients had been heavily pretreated with one or more surgical procedures (100%), radiotherapy (60%) and medical therapy (100%). In particular, they had all been treated with imatinib in monotherapy with signs of response in seven cases (70%), followed by secondary progression; three had received nilotinib also and seven imatinib and cisplatinum. One of them had previously received sirolimus in monotherapy with progression after 3 months (patient 6, Figure 2). Surgery was unfeasible in all cases. All patients but one were symptomatic for pain and/or functional impairment requiring constant treatment in six cases. In all patients, there was evidence of PD within the 6 months before starting treatment.

**drug delivery and toxicity**

The mean duration of treatment was 9 months (range 11-15 months). All patients started treatment with imatinib 400 mg/day and sirolimus 2 mg/day, continuously. In all cases of treatment interruption, both drugs were stopped and restored together. None reduced the dose of imatinib, while the dose of sirolimus was confirmed or modified according to the serum level. In particular, the final dose of sirolimus was 2 mg/day in five cases, 1.5 mg/day in two and 3.5 mg/day in another one. Overall, imatinib plus low-dose sirolimus treatment was well tolerated. The major non-hematologic toxic effects include mucositis (three cases, G2), infections (five cases, one G3) and in particular pneumonia (one patient), tumor abscess (one patient), herpes zoster (one case), herpes simplex (two patients), recurrent urinary tract infections (one patient, G2), diarrhea (one patient, G2) and lower limbs edema (one patient, G2). The most common hematologic toxic effects were neutropenia (five patients, G3 in two cases), chronic anemia (seven patients, no G34) and thrombocytopenia (two patients, no G34) (Table 2).

*Figure 2.* Pretreatment immunohistochemistry analysis positive for S6 and pS6 (A). After 3 months of treatment, magnetic resonance imaging (MRI) showed a RECIST stable disease [(B) baseline, (C) +3 months)]. In spite of no change in size, there was a >10% decrease in contrast enhancement, consistent with a response according to Choi’s criteria applied to MRI.
Treatment interruption for hematologic G3 toxicity was required in two patients while for non-hematologic ≥G2 adverse events in five cases, all resolved after discontinuation.

response

Nine patients are assessable for response (one early interruption). All of them were progressive before starting treatment. At 3 months, according to RECIST, one had a PR (Figure 1), seven had a stable disease (SD) (Figure 3) and one had a PD. According to Choi’s criteria, seven patients had a PR, with a ≥10% decrease in size in four cases, one was stable and one was progressing. MRI results were consistent with CT scan. A PET response was detectable in seven cases (Figures 1, 2 and 4), corresponding to those with Choi’s PR. The clinical benefit defined as RECIST complete response (CR) + PR + SD maintained ≥6 months was 89% (eight of nine patients) [23].

Patient 5 was still stable at 9 months according to RECIST, but he was progressing according to Choi’s criteria, PET scan and symptoms, so he stopped his treatment. Of four patients on treatment for >12 months, three are still responding. The fourth one, patient 3, had a minor progression after 12 months according to PET scan. A Choi’s PD was detectable on CT scan after 15 months. Even if the progression was not a RECIST PD, the patient’s symptoms got worse and he stopped his therapy. One responsive patient had to withhold temporarily her treatment because of an extensive abscess that arose in the site of her chordoma (Figure 4) at 6 months. At that time, she also had local pain, fever, leukocytosis and P-reactive protein increase, without any evidence of PD. The abscess was treated with drainage (150 ml pus) and antibiotics. Imatinib and sirolimus were discontinued for 3 months until complete recovery was obtained (no evidence of PD when treatment restored). The patient has restarted treatment for ~6 months, with no more complications and again response on MRI and PET scan.

All patients but two referred an improvement in symptoms present at baseline.

discussion

We treated 10 patients with advanced imatinib-resistant chordoma by adding sirolimus to imatinib. In nine of them, pretreatment material for the analysis was available and biochemical analysis provided evidence of mTOR pathway activation. In most patients, we saw a tumor response according to Choi’s criteria, along with a PET response and symptoms’ improvement. Of interest, one RECIST PR was observed and the other three patients showed minor dimensional responses. One patient had also received sirolimus as a single agent with progression, while she responded when imatinib was added. A biopsy taken after 8 weeks of treatment in the patient with a RECIST PR showed that the mTOR downstream effector, the ribosomal protein S6, was inactivated, while it was phosphorylated beforehand.

These preliminary observations point to some effectiveness of the combination of imatinib with an mTOR inhibitor in chordomas. The number of patients is low, and this was not a prospective clinical study. Thus, what is reported in this
article should prompt a phase II clinical study on the combination to assess its actual value in such a rare disease.

On imatinib as a single agent, most responses are not dimensional and their duration is generally slightly less than 1 year [12], while in the present series we had one PR according to RECIST and three minor responses. Thus, it is indicated by these early observations that adding sirolimus to imatinib may strengthen the activity of the latter. This may have important clinical implications in such a rare disease, for which an unmet clinical need clearly exists. Furthermore, the duration of response seems to be quite long, lasting >1 year in some patients.

Our evidence is thus based on a degree of tumor shrinkage but more strikingly on tumor response assessed through modified Choi criteria. In GIST, these criteria were clearly shown to correlate with the outcome much better than RECIST. We adapted Choi criteria and tested them in a series of STS patients treated with neoadjuvant chemotherapy, by correlating them with pathological response [21]. Again, modified Choi criteria better correlated with pathological response than RECIST. In clinical studies, the alternative is obviously to look at progression-free survival [23]. However, in an exploratory setting as this, tumor response is of course more useful. None the less, we also saw an interesting progression-free survival rate at 6 months.

We previously provided evidence that the antitumor activity of imatinib in chordomas may be related to the inhibition of PDGFRB that is activated through an autocrine/paracrine loop
In this series of heavily pretreated patients, with advanced and disabling disease (PS ≥ 2 in half the cases), the toxicity of the combination was acceptable. Main complaints were mucositis, and infectious opportunistic events, as expected using mTOR inhibitors [17]. In all cases of infections, these resolved after treatment discontinuation and possibly antibiotics/antiviral treatment. Interestingly, in one case, the tumor response was complicated by an abscess after 6 months. This reminds us of the first chordoma patient we treated with imatinib in 2002, who also showed a kind of liquefaction of the tumor after months of treatment [12]. Similarly, complicated responses are well known for GIST patients treated with imatinib.

As far as the treatment schedule is concerned, we decided to keep the blood level of sirolimus in the high-dose range used in transplanted patients, where the agent prevents graft rejection. Of course, this choice was empirical and clearly needs to be proved. Furthermore, significant variability in the oral absorption and bioavailability of sirolimus across patients and in the patient is reported, as we could experience as well [29,30]. The combination of sirolimus and imatinib might complicate the overall metabolic picture. In fact, sirolimus bioavailability and clearance are dependent on intestinal and hepatic metabolism by CYP 3A4 enzyme, which is the same system that metabolizes imatinib. This prompted us to regularly assess sirolimus blood levels and make dose adjustments accordingly. In our series, in most patients, the target-rapamycin-concentration (15–20 ng/ml) was reached by using the starting dose of 2 mg/day. However, in one patient, we had to increase the dose to 3.5 mg/day, while in two patients, it had to be reduced to 1.5 mg/day. Further studies are needed to optimize the scheduling. In this respect, continuous mTOR inhibition by rapalogs may also induce feedback AKT activation through the PI3K/IGFR pathway, as demonstrated in non-small-cell lung cancer, breast cancer and rhabdomyosarcoma cell lines and xenografts [17,31], thus attenuating potential antitumor activity. Possibly, a pulsating regimen might be better on the long run. Therefore, studies on recently set-up chordoma xenograft models have been planned.

In brief, what we observed strongly indicates to further investigate the combination of imatinib and sirolimus in advanced chordoma. Molecular targeted therapy is clearly of potential value in this rare disease, as documented by the use of imatinib alone. The long-term prognosis for chordoma patients, as well as the feasibility of more conservative local treatments, might take huge benefit from an effective medical therapy.

funding
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acknowledgements
Conflict of interest: AG, PGC and AM received honoraria for speaker’s bureau and compensations for advisory boards from Novartis Pharma. FC is married to a full-time officer employed by Novartis Pharma.

references