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Original article

Multicenter Phase II trial assessing effectiveness of imatinib mesylate on relapsed or refractory KIT-positive or PDGFR-positive sarcoma

Hideshi Sugiura[1], Yasuhiro Fujiwara[2], Masashi Ando[2], Akira Kawai[3], Akira Ogose[4], Toshifumi Ozaki[5], Ryohei Yokoyama[6], Toru Hiruma[7], Takeshi Ishii[8], Hideo Morioka[9], and Hideo Mugishima[10]

[1] Department of Orthopaedic Surgery, Aichi Cancer Center Hospital, 1-Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
[2] Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan
[3] Department of Orthopaedic Surgery, National Cancer Center Hospital, Tokyo, Japan
[4] Department of Orthopaedic Surgery, Niigata University, Niigata, Japan
[5] Department of Orthopaedic Surgery, Okayama University, Okayama, Japan
[6] Department of Orthopaedic Surgery, Kyusyu Cancer Center, Fukuoka, Japan
[7] Department of Orthopaedic Surgery, Kanagawa Cancer Center, Kanagawa, Japan
[8] Department of Orthopaedic Surgery, Chiba Cancer Center, Chiba, Japan
[9] Department of Orthopaedic Surgery, Keio University, Tokyo, Japan
[10] Department of Pediatrics, Nihon University, Tokyo, Japan

Abstract

Background. Imatinib myselate is a molecularly targeted drug that inhibits Abl tyrosine kinase, as well as type III tyrosine kinase receptors such as platelet-derived growth factor receptor (PDGFR), KIT, colony-stimulating factor 1 receptor (CSF-1R), and discoidin domain receptor (DDR). Ph1 chromosome-positive chronic myeloid leukemias (CMLs), KIT-positive gastrointestinal stromal tumors (GISTs), and PDGFR-positive dermatofibrosarcoma protuberans (DFSP) have been reported to be responsive to imatinib treatment. We conducted a multicenter Phase II trial of imatinib in patients with relapsed or refractory KIT-positive (excluding GISTs) or PDGFR-positive sarcomas.

Methods. Patient ages ranged from 12 and 75 years. Eligibility criteria included (1) metastatic sarcomas with a definitive diagnosis based on histopathology or that were completely unresectable and locally advanced; (2) relapsed or refractory cases that had completed standard treatment; and (3) a tumor confirmed by immunohistochemical staining to be KIT- or PDGFR-positive. A 600-mg dose of imatinib was administered to patients once a day, with each patient receiving six courses of the drug and each course lasting 4 weeks. In cases categorized as stable or progressive, the imatinib dose was increased to 800 mg/day administered twice daily.

Results. A total of 25 patients who met the eligibility criteria were enrolled in the trial; 22 were evaluated for response. The response rate with a 600 mg/day dose of imatinib was 4.5% (0 complete response, 1 partial response). There were no other objective responses after increasing imatinib to 800 mg/day (0/10). We estimated 50% progression-free survival to be 61.0 days for an imatinib dose of 600 mg/day based on the Kaplan-Meier method. Side effects of imatinib were generally similar to those observed in previous clinical trials.

Conclusions. Our results did not indicate effectiveness of imatinib monotherapy at a dose of 600 or 800 mg/day in patients with relapsed or refractory KIT-positive (excluding GISTs) or PDGFR-positive sarcomas. Our findings suggest the need to evaluate the synergistic effect of combination therapy with other anticancer drugs.

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Introduction

Bone and soft tissue sarcomas account for approximately 0.9% of malignant tumors in adults. In the United States, about 10400 and 2400 people a year are found to have soft tissue sarcoma and bone sarcoma, respectively.[1] Unresectable locally advanced and distant metastasis of bone and soft tissue sarcomas are, at present, rarely treatable. Additionally, no effective drug exists for relapsed or refractory cases after standard treatments (e.g., anticancer drugs, radiation therapy) have been used.[2,3]

Imatinib mesylate (Glivec, STI-571) is a molecularly targeted drug that inhibits Abl tyrosine kinase and several type III tyrosine kinase receptors, such as platelet-derived growth factor receptor (PDGFR), KIT, colony-stimulating factor 1 receptor (CSF-1R), and discoidin domain receptor (DDR).[4] Clinically, disorders responding to imatinib treatment include Ph1 chromosome-positive chronic myeloid leukemia (CML),[5] KIT-positive gastrointestinal stromal tumors (GISTs),[6] and PDGFR-positive dermatofibrosarcoma protuberans (DFSP).[7] Many studies[8–19] have shown that KIT is expressed in osteosarcoma, synovial sarcoma, eosinophilic granuloma, and neuroblastoma[8–11] and that PDGF ligands and receptors are expressed in osteosarcomas, desmoplastic small round cell tumors (DSRCTs), and synovial sarcomas.[8,12–19] Furthermore, a tumor growth-

inhibiting effect in cell lines derived from Ewing sarcoma and neuroblastoma has been observed in vitro.[20,21] In tumors expressing KIT and PDGFR, we expect imatinib, which targets both kinases, to inhibit tumor growth.

The aim of the present study was to evaluate the effectiveness and safety of imatinib in patients with KIT-positive (excluding GISTs) or PDGFR-positive locally advanced or metastatic sarcomas that have relapsed after standard treatment. This study was conducted at nine Japanese university hospitals and facilities specializing in cancer.

Subjects and methods

Eligibility criteria

Patients with osteosarcoma, neuroblastoma, Ewing's sarcoma/primitive neuroectodermal tumor (PNET), DSRCT, rhabdomyosarcoma, liposarcoma, fibrosarcoma, angiosarcoma, synovial sarcoma, malignant fibrous histiocytoma (MFH), malignant peripheral nerve sheath tumor (MPNST), leiomyosarcoma, clear cell sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, and other sarcomas excluding GIST were considered for this study. The enrollment period was March 2005 to September 2006. To be eligible, certain criteria had to be met: The patient had to have (1) a metastatic sarcoma that had a definitive diagnosis based on histopathology or was locally advanced and could not be completely resected; (2) have relapsed or refractory disease that had undergone completed standard treatment (however, patients with new-onset epithelioid sarcoma or alveolar soft part sarcoma were also eligible); (3) a tumor confirmed through immunohistochemical staining to be KIT (CD117)- or PDGFR-positive; (4) the availability of a usable tumor tissue block based on collective diagnosis by three pathologists; and (5) at least one measurable lesion that was ≥20 mm [however, for spiral computed tomography (CT), patients with a confirmed lesion of ≥10 mm were also eligible].

Patients needed to (1) be 12–75 years of age; (2) have a European Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; (3) have a life expectancy of ≥3 months; (4) have proper organ function (neutrophil cell count of ≥1000/mm^3, platelet count of ≥100 000/ mm^3, maximum aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) levels of 60 IU/l, total maximum bilirubin of 1.5 mg/dl, and maximum serum creatinine level of 1.5 mg/dl; (5) have an electrocardiogram showing normal heart function with no abnormalities that require treatment; (6) be class 1 based on the New York Heart Association (NYHA) classification; (7) have recovered from antecedent treatment (chemotherapy); (8) have no uncontrollable active infections; (9) not be pregnant or nursing; (10) have no brain metastases with clinical manifestations. Only patients who fulfilled these selection criteria were included in the study. This study was approved by the institutional review board, and informed consent was obtained from each patient.

Study design

We separated cases into four categories based on changes in tumor size as follows: (1) complete remission (CR) — disappearance of target lesions and secondary changes resulting from the tumor; (2) partial remission (PR) — 30% or greater reduction in the sum of the longest diameters of target lesions compared to before commencing treatment; (3) progressive disease (PD) — 20% or greater increase in the sum of the longest diameters of target lesions; and (4) stable disease (SD) — neither tumor reduction of CR or PR nor tumor increase of PD.

A 600 mg dose of imatinib was administered to patients once per day. Each patient received six courses of the drug, with each course lasting 4 weeks (28 days). We evaluated the tumor regression effect by CT (5 mm slice or spiral CT) or magnetic resonance imaging (MRI) after every two cycles of drug administration. If the case was categorized as SD or PD, the dose was increased to 800 mg per day administered twice daily. If the tumor regression effect was classified as PR or CR after this increase, we repeated the treatment for the full six courses (24 weeks).

Our primary endpoint was the tumor regression effect after a daily imatinib dose of 600 mg. The secondary endpoint was the tumor regression effect after the increased dose of 800 mg/day. We evaluated the frequency and degree of adverse event occurrence using progression-free survival based on the 600 mg dose treatment.

KIT and PDGFR immunohistochemical staining

After deparaffinization and hydrophilicization, we conducted antigen retrieval using a warm bath (Target Retrieval Solution, pH 6.0, code no. S1699/S1700; Dako, Glostrup, Denmark). For KIT staining, we used anti-human CD117/KIT polyclonal rabbit antibody (1:100; code no. A4502; Dako) in citric acid buffer 10 mmol/l (pH 6.0), heated in an autoclave for 5 min at 121°C. For PDGFR staining, we used the same procedure with anti-human PDGFR alpha polyclonal rabbit antibody (1:100; cat. no. RB-1691; NeoMarkers, Fremont, CA, USA) and a heating time of 10 min in the autoclave. We used normal rabbit immunoglobulin as a negative control. We blocked endogenous peroxidase (code no. S2001/S2023; Dako) and used the rabbit primary anti-

body-based EnVision+ polymer reagent (code no. K4002/K4003; Dako) for the detection system. Finally, we used a chromogenic substrate solution (DAB+ basic kit, code no. K3467/K3468; Dako) for development. We rated the staining intensity of KIT and PDGFR alpha using a four-step scale: 0 for no staining, 1+ for a weakly positive, 2+ for moderately positive, and 3+ for strongly positive.

Statistical methods

At present, no effective drug exists to treat cases of relapsed or refractory sarcomas examined in this clinical trial. The monotherapy response rate for sarcomas currently ranges from 10% to 30%. A 30% response rate for tumor regression obtained with imatinib monotherapy suggests promising clinical effectiveness. Accordingly, we set the expected response rate of tumor regression to 30% in this trial, based on a 600 mg/day dose of imatinib. With a threshold response rate of 10%, α (type I error) = 0.05, and β (type II error) = 0.15, the required number of cases needed in the study was at least 35. Thus, we planned to enroll 40 subjects in the trial. We constructed an accurate 95% confidence interval (CI) based on response rates on an F distribution. Imatinib was considered effective if the lower limit of this 95% CI exceeded the threshold response rate of 10%; otherwise, the treatment was considered ineffective. Furthermore, we used the Kaplan-Meier method to estimate the progression-free survival function and 50% progression-free survival.

To assess adverse events, we performed an evaluation during the first, second, and fourth weeks of the first course of imatinib treatment. For the second through sixth courses, we continued evaluation during the second and fourth weeks only. We graded adverse events according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 scale. We recorded the highest grade during each treatment course and further investigated grade 3 and 4 adverse events thought to be related to imatinib. For patients suffering from grade 3 or 4 events, administration of imatinib was halted and resumed at the same dose only if the patient recovered within a week. In cases where recovery took longer than 1 week, treatment was resumed at a reduced dose of 200 mg per day.

This study was performed in accordance with the Good Clinical Practice (GCP) guideline[22] laid down by the revised Pharmaceutical Affairs Act in Japan.[23]

Results

During the study enrollment period, 31 of 49 patients were deemed eligible based on results of KIT and PDGFR immunohistochemical staining and collective pathological diagnosis. Of these, 25 were enrolled in the study. One patient completed all six treatment courses (24 weeks), 13 patients discontinued treatment by the end of two courses, and the remaining 11 discontinued treatment by the end of four courses. The primary reason for early discontinuation was exacerbation of the present illness, with the most common evaluation (17 subjects) being "treatment ineffective." In addition, three patients refused to continue treatment for reasons unrelated to adverse events, three discontinued treatment due to adverse events, and one left the study because of exacerbated psychological symptoms.

Although 25 patients were administered imatinib, 3 patients were excluded from analysis of treatment effectiveness. Two of these patients were found to be ineligible for the study after enrollment. GCP was not adhered to in the third patient. Nevertheless, all 25 patients were included in the safety evaluation of imatinib (Table 1).

Response analysis

The response rate with a 600 mg daily dose of imatinib was 4.5% (1/22: 0 CR, 1 PR). The 95% CI ranged from 0.1% to 22.8%, with the lower limit falling below the 10% threshold response rate. Based on this result, we determined that no tumor regression effect could be demonstrated from the daily imatinib dose of 600 mg (Table 2). The response rate after increasing imatinib administration to 800 mg per day was 0% (0/10). The 95% CI ranged from 0% to 30.8%, with the lower limit falling below the 10% threshold response rate. Thus, similar to the above result, we concluded that no tumor regression effect could be seen from the dose of 800 mg per day (Table 3). We estimated 50% progression-free survival to be 61.0 days for a daily imatinib dose of 600 mg based on the Kaplan-Meier method to examine progression-free survival (Fig. 1).

Only one patient, who had synovial sarcoma, exhibited a tumor regression effect of at least PR. In this patient, tumor size before treatment initiation was 3.0 cm. This was smaller than in the other four synovial sarcoma cases (6.5–20.5 cm), in which treatment was deemed ineffective.

Safety Analysis

Adverse events considered related to imatinib occurred in all 25 cases. Nausea, reported in 72.0% (18/25) of cases, was the most common side effect. Other adverse events included anemia, edema, and emesis (68.0% for each, 17/25 cases); fatigue (60.0%, 15/25 cases); and neutropenia, loss of appetite, and hypophosphatemia (52.0% for each, 13/25 cases). The incidence of grade 3

Table 1. Patient characteristics

Characteristic	Response analysis	Safety analysis
Sex		
Male	12 (54.5%)	13 (52.0%)
Female	10 (45.5%)	12 (48.0%)
Age		
Average ± SD	43.0 ± 19.79	42.0 ± 19.71
Median	36 (14–71)	36 (14–71)
Performance status		
0	13 (59.1%)	16 (64.0%)
1	7 (31.8%)	7 (28.0%)
2	2 (9.1%)	2 (8.0%)
Subtype		
Osteosarcoma	2 (9.1%)	2 (8.0%)
Ewing/PNET	4 (18.2%)	4 (16.0%)
Rhabdomyosarcoma	0	1 (4.0%)
Liposarcoma	0	1 (4.0%)
Fibrosarcoma	4 (18.2%)	4 (16.0%)
Synovial sarcoma	5 (22.7%)	6 (24.0%)
MFH	1 (4.5%)	1 (4.0%)
Epithelioid sarcoma	2 (9.1%)	2 (8.0%)
Others	4 (18.2%)	4 (16.0%)
Operation		
−	3 (13.6%)	4 (16.0%)
+	19 (86.4%)	21 (84.0%)
Chemotherapy		
−	3 (13.6%)	4 (16.0%)
+	19 (86.4%)	21 (84.0%)
Irradiation		
−	15 (68.2%)	15 (60.0%)
+	7 (31.8%)	10 (40.0%)
Distant metastasis		
−	2 (9.1%)	4 (16.0%)
+	20 (90.9%)	21 (84.0%)
KIT		
0	14 (63.6%)	16 (64.0%)
+1	6 (27.3%)	7 (28.0%)
+2	1 (4.5%)	1 (4.0%)
Unknown	1 (4.5%)	1 (4.0%)
PDGFR		
0	0	1 (4.0%)
+1	16 (72.7%)	18 (72.0%)
+2	1 (4.5%)	1 (4.0%)
Unknown	5 (22.7%)	5 (20.0%)
Total no.	22	25

PNET, primitive neuroectodermal tumor; MFH, malignant fibrous histiocytoma; PDGFR, platelet-derived growth factor receptor

and 4 adverse events was as follows: hypophosphatemia (32.0%, 8/25 cases); neutropenia (16.0%, 4/25 cases); and anemia (12.0%, 3/25 cases) (Table 4). Two deaths occurred within 30 days after treatment completion. However, in both of these cases, mortality was due to exacerbation of the primary disease, and no relation to the clinical trial drug was found.

Discussion

We evaluated the effectiveness and safety of imatinib on KIT-positive (excluding GISTs) or PDGFR-positive

Table 2. Response to a 600 mg/day dose of imatinib in patients with relapsed or refractory KIT- or PDGFR-positive sarcoma

Histology	No.	CR	PR	SD	PD	NE
Synovial sarcoma	5	0	1	1	1	2
Ewing sarcoma	4	0	0	1	3	0
Fibrosarcoma	4	0	0	1	2	1
Osteosarcoma	2	0	0	0	1	1
Epithelioid sarcoma	2	0	0	1	1	0
Chondrosarcoma	2	0	0	1	0	1
MFH	1	0	0	0	1	0
DFSP	1	0	0	1	0	0
Chordoma	1	0	0	0	0	1
Total	22	0	1	6	9	6

CR, complete remission; PR, partial remission; PD, progressive disease; SD, stable disease; NE, not evaluable; MFH, malignant fibrous histiocytoma; DFSP, dermatofibrosarcoma protuberans

Table 3. Response to an 800 mg/day dose of imatinib in patients with relapsed or refractory KIT- or PDGFR-positive sarcoma

Histology	No.	CR	PR	SD	PD	NE
Synovial sarcoma	1	0	0	0	1	0
Ewing sarcoma	2	0	0	0	2	0
Fibrosarcoma	0	0	0	0	0	0
Osteosarcoma	2	0	0	0	0	2
Epithelioid sarcoma	2	0	0	1	1	0
Chondrosarcoma	1	0	0	1	0	0
MFH	1	0	0	0	1	0
DFSP	1	0	0	1	0	0
Chordoma	0	0	0	0	0	0
Total	10	0	0	3	5	2

locally advanced or metastatic sarcomas. We performed PDGFR and KIT immunostaining and used imatinib only in cases that showed positive staining. However, among the 22 patients who received imatinib at 600 mg per day, none was evaluated as CR, one as PR, six as SD, and nine as PD (response rate 4.5%, 1/22). We found no tumor regression effect based on a daily dose of 600 mg of imatinib. Additionally, no effect was observed even after increasing the dose to 800 mg per day.

In a study by Bond et al.,[24] imatinib 440 mg/m^2 was administered to children with relapsed, progressive osteosarcoma, Ewing sarcoma, synovial sarcoma, DSRCT, neuroblastoma, or GIST. The authors found that among the 59 cases evaluated 52 were deemed to have PD; only one patient with Ewing sarcoma had a PR (response rate of 1.7%, 1/59). Bond et al. concluded that imatinib 440 mg/m^2 was enough to inhibit the phosphorylation of PDGFR and KIT but insufficient to inhibit the tumor.

Although we did not conduct a pharmacokinetic examination, a 440 mg/m^2 dose of imatinib is equivalent to 600 mg in the body. Additionally, our results are con-

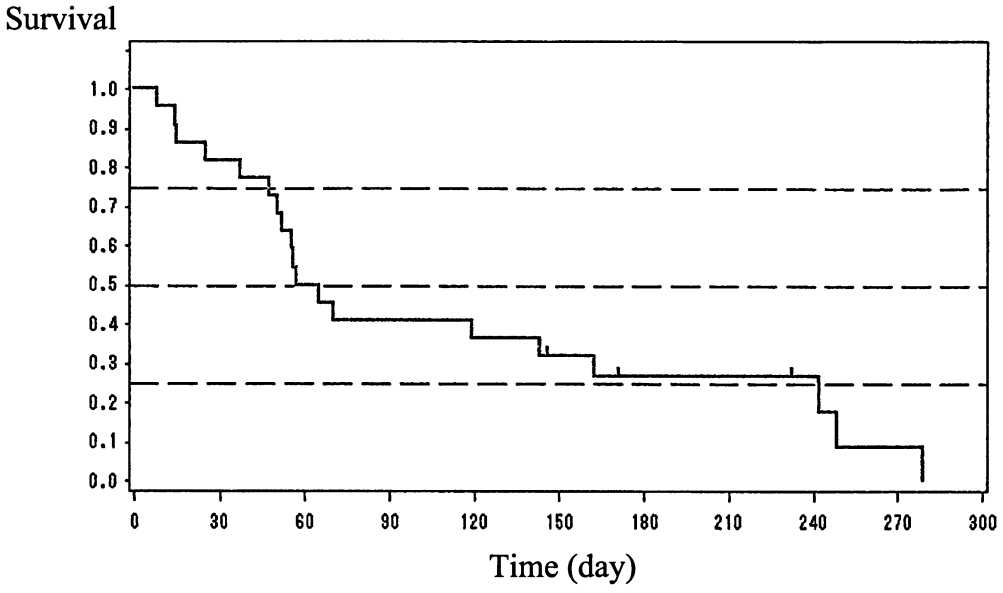

Fig. 1. Kaplan-Meier progression-free survival curve for patients with relapsed or refractory KIT- or PDGFR-positive sarcoma. Evaluation for tumor status was performed by computed tomography (5-mm slice or spiral) or magnetic resonance imaging after every two cycles of drug administration. The 50% progression-free survival was 61.0 days for an imatinib dose of 600 mg/day

Table 4. Adverse events potentially related to imatinib

Toxicity	Total no.	Grade			
		G1	G2	G3	G4
Hematological					
Anemia	17 (68.0%)	7 (28.0%)	7 (28.0%)	3 (12.0%)	0
Thrombocytopenia	9 (36.0%)	6 (24.0%)	2 (8.0%)	1 (4.0%)	0
Neutropenia	13 (52.0%)	6 (24.0%)	3 (12.0%)	3 (12.0%)	1 (4.0%)
Leukopenia	12 (48.0%)	2 (8.0%)	8 (32.0%)	2 (8.0%)	0
Nonhematological					
Edema	17 (68.0%)	8 (32.0%)	8 (32.0%)	1 (4.0%)	0
Fatigue	15 (60.0%)	12 (48.0%)	2 (8.0%)	1 (4.0%)	0
Loss of appetite	13 (52.0%)	10 (40.0%)	3 (12.0%)	0	0
Nausea	18 (72.0%)	15 (60.0%)	2 (8.0%)	1 (4.0%)	0
Emesis	17 (68.0%)	16 (64.0%)	1 (4.0%)	0	0
Hypophosphatemia	13 (52.0%)	0	5 (20.0%)	8 (32.0%)	0

sistent with the findings of Bond et al.[24] Chugh et al.[25] also evaluated the tumor regression effect based on 600 mg of imatinib per day on 10 types of sarcoma in 185 patients. They observed that 28 patients (15.1%) showed a clinical benefit response, including those with SD. However, only one case was evaluated as CR and three as PR (response rate 2.2%, 4/185). Heinrich et al.[26] reported four cases of CR and nine cases of PR among 102 cases (response rate 12.8%, 13/102), but the four CR cases and six of the PR cases were patients with DFSP. Table 5 summarizes response rates to imatinib by sarcoma subtype among the published cases from Bond et al.[24] Chugh et al.[25] and Heinrich et al.[26] along with the current study. Although we assessed response rates for a variety of tumors, all rates appeared to be between 0% and 10% except for DFSP. No tumor types, aside from DFSP, were found to be responsive to imatinib.

In the studies by Bond et al.[24] and Chugh et al.,[25] expression of PDGFR or KIT was not considered; and thus the connection with PDGFR and KIT was not discussed. In the current study, we examined the effectiveness of imatinib on KIT- or PDGFR-positive locally advanced or metastatic sarcoma. However, we did not find a correlation between KIT or PDGFR and the effectiveness of imatinib. This result is consistent with past research on metastatic melanoma,[27] small-cell lung cancer,[28] and metastatic breast cancer,[29] which express PDGFR and KIT. Heinrich et al.[26] previously evaluated

Table 5. Response rates to imatinib by sarcoma subtype

Histology	No.	CR	PR	Response rate[a] (%)
Synovial sarcoma	46	0	2	4.3
Ewing sarcoma	45	0	1	2.2
Fibrosarcoma	16	0	1	6.2
Osteosarcoma	40	0	0	0
Epithelioid sarcoma	2	0	0	0
Chondrosarcoma	9	0	0	0
MFH	31	0	1	3.2
DFSP	13	4	6	76.9
Chordoma	6	0	0	0
Leiomyosarcoma	40	1	0	2.5
Liposarcoma	42	0	1	2.4
Angiosarcoma	18	0	0	0
Rhabdomyosarcoma	4	0	0	0
Aggressive fibromatosis	20	0	2	10
DSRCT	15	0	0	0
Neurofibrosarcoma	3	0	0	0
MPNST	7	0	0	0
GIST	1	0	0	0
Neuroblastoma	10	0	0	0
Total	368	5	14	5.2

These data were calculated for the published cases integrated with data from the current study

[a]Rate of patients who had a complete or partial response to imatinib

DFSP, dermatofibrosarcoma protuberans; DSRC, desmoplastic small round cell tumor, MPNST, malignant peripheral nerve sheath tumor; GIST, gastrointestinal stromal tumor

the correlation between expression of KIT, PDGFRA, and PDGFRB kinases and the clinical responsiveness to imatinib in 186 tumor cases. They found no correlation and observed that only DFSP, hypereosinophilic syndrome, myeloproliferative disorder, and systemic mastocytosis showed a clinical responsiveness above PR. In sarcomas other than GIST[6] and DFSP,[7] imatinib monotherapy rarely exhibits a tumor regression effect. Thus, there is a need to evaluate the synergistic effect of combination therapy using other anticancer drugs.[30]

In this study, side effects from imatinib were generally similar to those observed in previous clinical trials.[24–29] We considered the side effects acceptable while being mindful of bone marrow suppression and edema.

Conclusion

Our findings indicate that imatinib monotherapy at 600 or 800 mg/day in patients with relapsed or refractory KIT-positive (excluding GISTs) or PDGFR-positive sarcoma was ineffective.

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There were no potential conflicts of interest to be disclosed.

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