Target Therapy of Unresectable or Metastatic Dermatofibrosarcoma Protuberans With Imatinib Mesylate

An Analysis on 22 Chinese Patients

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Abstract:
Dermatofibrosarcoma protuberans (DFSP) is a rare, plaque-like tumor of the cutaneous tissue occurring more on the trunk than the extremities and neck. More than 95% of DFSP present anomalies on the 17q22 and 22q13 chromosomal regions leading to the fusion of COL1A1 and PDGFB genes. Surgery is the optimal treatment for DFSP, but less effective in locally advanced or metastatic patients, as is the case with chemotherapy and radiotherapy. The aim of this study was to assess retrospectively the therapeutic activity and safety of imatinib on 22 Chinese patients with locally inoperable or metastatic DFSP at a single institution.

In the collected data of 367 Chinese patients with DFSP, we analyzed retrospectively 22 patients with locally advanced or metastatic DFSP, all of whom received imatinib therapy at 1 center from January 2009 to October 2014. Patients were administered with imatinib at an initial dose of 400 mg and escalated to 800 mg daily after they developed imatinib resistance. The median follow-up time was 36 months, and the median treatment time was 15 months.

The results showed that 10 locally advanced DFSP patients and 12 metastatic DFSP patients received imatinib therapy. Apart from 1 patient who developed primary imatinib resistance, 15 patients achieved partial remission (PR), and 6 patients achieved stable disease (SD). Both fibrosarcomatous DFSP and classic DFSP patients demonstrated similar response to imatinib. Median PFS was estimated to be 19 months. Median overall survival (OS) has not been reached, and estimated 1- and 3-year OS rates were 95.5% (21/22) and 77.3% (17/22), respectively. Four out of 10 patients with primarily unresectable DFSP received complete surgical resection after neoadjuvant treatment of imatinib.

Imatinib therapy is well tolerated with a safety profile and is the therapy of choice in locally inoperable or metastatic DFSP. Neoadjuvant treatment of locally advanced or metastatic DFSP with imatinib improves surgical outcomes and may facilitate resection of difficult tumors.

Abbreviations:
DFSP = dermatofibrosarcoma protuberans, FS-DFSP = fibrosarcomatous DFSP, GIST = gastrointestinal stromal tumors, OS = overall survival, PD = progressive disease, PFS = Progression-free survival, PR = partial remission, SD = stable disease.

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare, nodular, or plaque-like tumor of the cutaneous tissue occurring more on the trunk, than in proximal extremities, and rarely in the head and neck region. Although DFSP is characterized by a high rate of local recurrence, metastatic diseases are very rare (<5%). More than 95% of DFSP present anomalies on the 17q22 and 22q13 chromosomal regions leading to the fusion of COL1A1 and PDGFB genes. The result of this rearrangement is the upregulation of a COL1A1–PDGFB fusion protein, which leads to autocrine or paracrine activation of the PDGF receptor from the production of its functional ligand and thus to cellular proliferation.4,5 Because DFSP is similar to some other diseases, immunohistochemical studies are necessary to establish diagnosis. If immunohistochemical studies fail to detect the difference between DFSP and other histologically similar tumors, cyto genetic testing for the characteristic translocation t(17;22)(q11;22) can contribute to the diagnosis.

Wide local excision or Mohs micrographic surgery (MMS) with precise histological margin control is the gold standard treatment for DFSP. Surgical resections with wide margins of 2 to 3 cm are recommended owing to the relatively high risk of local recurrence (up to 50%),6 but MMS can achieve tumor clearance with smaller margins and greater preservation of healthy tissue compared with wide local excision.7 However, such margins are generally hard to obtain due to the anatomical location of the tumor, and radical excision may cause functional or cosmetic disfigurement, in which incorporation of multimodality approaches including reconstructive techniques is often needed. Radiotherapy as a sole modality in unresectable cases has limited value,8 as is the case with cytotoxic chemotherapy in advanced cases.9

As the molecular pathogenesis of DFSP was elucidated, imatinib target therapy, which is a tyrosine kinase inhibitor specifically directed at BCR/ABL, KIT, and PDGFR-α and PDGFR-β, was introduced into the treatment of DFSP.9 In the study B2225, 10 patients with locally advanced or metastatic DFSP were treated with imatinib, all of whom showed responses to imatinib, including complete responses (CRs) in 5 out of 10 advanced cases and 1 partial remission lasting 7 months in metastatic cases.10 As a consequence, imatinib was registered as a therapy of choice in unresectable or metastatic DFSP. The aim of this study was to assess retrospectively the
therapeutic activity and safety of imatinib on 22 Chinese patients with locally unresectable or metastatic DFSP at a single institution.

PATIENTS AND METHODS

From January 2009 to October 2014, we treated about 367 Chinese patients with DFSP, including surgery or medical therapy. Among them, metastasis occurred in 15 patients, and 12 out of 15 patients received imatinib treatment. In the collected data of 367 patients with DFSP, we analyzed retrospectively 22 patients with locally advanced or metastatic DFSP, all of whom received imatinib therapy at the Department of Soft Tissue Sarcoma in Fudan University Shanghai Cancer Center.

According to our institutional protocol for locally advanced gastrointestinal stromal tumors (GIST), all patients with unresectable or metastatic DFSP were commenced on imatinib therapy at an initial dose of 400 mg/d orally. The 10 unresectable cases were all evaluated by 2 different oncologic surgeons. Once the patient had been evaluated with progressive disease (PD) after being treated at the dose of 400 mg daily, we increased the dosage from 400 to 800 mg. The patients were administered with sunitinib after developing imatinib resistance.

Before beginning the therapy, patients were evaluated with history and physical examination, an adequate bone marrow and organ function to receive imatinib mesylate. All patients were in group performance status (Eastern Cooperative Oncology Group) >3. All cases had histologically confirmed DFSP in our center. A computed tomography or magnetic resonance imaging scan of the sites of diseases was also required. Tumor assessment was performed after 4 weeks from initiation of the treatment, and then every 3 months, in case of suspected progression, and before surgery. Response was evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST 1.0). The Fudan University Shanghai Cancer Center ethics committee approved the study.

Statistical Analyses

All statistical materials were computed by using SPSS software (version 16.0; SPSS, Chicago, IL). The analysis of survival curves was performed by using the Kaplan–Meier method. Progression-free survival (PFS) time was calculated from the beginning of imatinib therapy to the date of recent follow-up time, or disease progression or the death of the patient due to the disease. Overall survival (OS) time was calculated from the beginning of imatinib treatment to the date of the last follow-up or death of the patient due to the disease.

RESULTS

Patient Clinical and Pathological Data

The group consisted of 9 men and 13 women; median age at the beginning of imatinib therapy was 43 years (age range: 21–69 years). The primary tumors occurred on the trunk in 18 patients and extremity in 4 patients. Ten patients had a locally advanced DFSP not amenable to surgery, with the diameter of tumors being >10 cm and adjacent to the vital organ, such as mediastinum, where initial surgery would have caused unacceptable aesthetic results or without the probability of curative excision of the tumor. The other 12 patients were metastatic, including 7 patients metastatic to the lung (Figure 1A), 2 patients to distant soft tissue from the primary site, 1 to sternum and mediastinum (Figure 2A), 1 to brain, and 1 to lumbar vertebra. All patients had no lymph node metastasis. Before the beginning of imatinib therapy, 2 patients with primary large tumors received no resection, while the other 20 patients were recurrent and underwent numerous surgeries, ranging from 2 to 15 times. The detailed characteristics of the patients’ clinical and pathological data are demonstrated in Table 1.

Outcome of Imatinib Treatment

The median follow-up time was 36 months (range: 6–81 months), and the median treatment duration was 15 months (range: 1–43 months). One patient developed primary imatinib resistance at the first month of treatment, while 15 patients...
achieved partial remission (PR), and 6 patients achieved SD. Five patients with fibrosarcomatous DFSP (FS-DFSP), characterized clinically by an increased metastatic potential,12 were also responsive to imatinib therapy. The metastatic lesion in the left lung of 1 patient decreased remarkably as early as 39 days of therapy with imatinib (Figure 1). Overall clinical benefit of imatinib therapy (computed as the sum of PR and SD rates) was 95.5%. After imatinib neoadjuvant treatment from 1 to 6 months, the best responses were observed according to the RECIST criteria and 2 oncologic surgeons assessed the possibility of residual disease resection. In the 10 DFSP patients with unresectable disease, 4 patients received complete surgical resection, achieving an acceptable cosmetic result after neoadjuvant treatment of imatinib. One patient, in whom metastasis occurred to the sternum and mediastinum, received complete oncoplastic resection after 1 month of imatinib neoadjuvant treatment (Figure 2). After the radical resection, all 4 patients received adjuvant imatinib therapy for 1 year, which showed stable disease (SD) and no signs of recurrent or distant metastases after stopping imatinib treatment from 6 to 33 months.

In the 22 patients of this group, 3 metastatic patients received chemotherapy with the regimen of doxorubicin and ifosfamide, but all were evaluated as having no effect after 1 circle of chemotherapy. In the 21 imatinib-sensitive patients, 5 patients developed PD at the dose of 400 mg and crossed over to high dosage of 800 mg; 2 out of 5 patients achieved PR or SD again, including 1 patient who received local resistant nodule excision. The other 3 patients who showed no response to 800 mg of imatinib therapy switched to sunitinib treatment, after achieving transient disease control, then 1 transferred to nilotinib treatment, and the other 2 received imatinib again until death. The 2 patients received second imatinib therapy developed SD from 3 to 5 months. One patient was administered with nilotinib after sunitinib resistance, but with no impact on disease control. The details of imatinib treatment are demonstrated in Table 2.

PFS and OS curves for the entire group of patients are shown in Figures 3 and 4, respectively. Median PFS was estimated to be 19 months (range: 7–51 months). At the time of the analysis, 17 patients (77.3%) were alive. Median OS has not been reached, and estimated 1- and 3-year OS rates were 95.5% (21/22) and 77.3% (17/22), respectively.

**Treatment Toxicity**

Adverse events were common during imatinib treatment and affected 12 patients, and the majority of the events were

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**FIGURE 2.** Clinical photographs documenting partial remission of the metastatic lesion to sternum and mediastinum after imatinib neoadjuvant therapy, which underwent complete oncoplastic resection of residual disease (a) before therapy; (b) after 1 month of therapy with imatinib.

**TABLE 1. Patient Characteristics**

| Characteristics            | No. of Patients | Total (%) |
|----------------------------|-----------------|-----------|
| Gender                     | 22              | 100.0     |
| Male                       | 9               | 40.9      |
| Female                     | 13              | 59.1      |
| Age (y)                    | 43              | 21–69     |
| Primary tumor location     | 22              | 100.0     |
| Trunk                      | 18              | 81.8      |
| Extremities                | 4               | 18.2      |
| Classic DFSP               | 17              | 77.3      |
| Fibrosarcomatous DFSP      | 5               | 22.7      |
| Presentation               | 22              | 100.0     |
| Primary                    | 2               | 9.1       |
| Recurrent                  | 8               | 36.4      |
| Distant metastases         | 12              | 54.5      |
| Lung                       | 7               | 31.8      |
| Distant soft tissue        | 2               | 9.1       |
| Mediastinum                | 1               | 4.5       |
| Brain                      | 1               | 4.5       |
| Lumbar vertebra            | 1               | 4.5       |

| DFSP = dermatofibrosarcoma protuberans. |
mild. The most common were fluid retention/edema fatigue (45.5%; grade 1–10), nausea (50%; grade 1–11), skin toxicity (18.2%; grade 1–3 cases, grade 3–1), granulocytopenia (18.2%; grade 1–3, grade 2–1), and diarrhea (9.1%; grade 1–2 cases). Imatinib-related adverse events led to definitive drug withdrawal for 3 patients, including 2 patients who had drug-related rashes, and 1 patient who had grade 2 granulocytopenia. All grade 3 toxic events were manageable with standard supportive treatment or dose reduction for about 1 week.

**DISCUSSION**

Since the recent identification of the significance of PDGFR activation in the DFSP pathogenesis, the effectiveness of targeted therapy by inhibition of the PDGFR protein-tyrosine kinase has been evaluated. Imatinib mesylate is a tyrosine kinase inhibitor, which has also been found to be the first effective systemic therapy in DFSP. The inhibitory effect of imatinib on the growth of DFSP was described and ultimately led to its approval for locally advanced or metastatic DFSP.8,13 Tumor reduction began already at few weeks after treatment initiation, and remarkable decrease as early as 1 month was observed in our group (Figures 1B and 2B). In the present study, 1 patient developed primary imatinib resistance at the first month of the treatment, while 21 patients were responsive to imatinib therapy, with the reduction in painful tumors as early as a week after the treatment. Gronchi et al14 have suggested that FS-DFSP with t(17;22) are still imatinib sensitive although responses appear to last for a short term, while FS-DFSP lacking the specific aberration do not respond to the treatment.10 In our study, both classic DFSP and FS-DFSP patients had shown good response to imatinib therapy. It has also been shown that the presence of the molecular target (COL1A1–PDGFB fusion) appears to be the responsive marker to imatinib treatment in DFSP patients, and it is obligatory in every case before initiating the imatinib therapy.14 All patients in our study did not receive pretreatment evaluation by fluorescence in situ hybridization, which may be the limitation of our study. The patient experiencing primary imatinib resistance may according to be without r(17;22) or t(17;22) chromosomal rearrangements.

**TABLE 2.** Details of Target Therapy

| Characteristics | No. of Patients | Total (%) |
|-----------------|----------------|-----------|
| Progression status |               |           |
| Progression free  | 5              | 22.7      |
| Progression     | 17             | 77.3      |
| Best overall response |          |           |
| Partial remission | 15             | 68.2      |
| Stable disease   | 6              | 27.3      |
| Progression disease | 1            | 4.5       |
| Primary resistance | 1             | 4.5       |
| Secondary resistance | 5            | 22.7      |
| Dosage of imatinib |               |           |
| 400 mg/d        | 17             | 77.3      |
| 800 mg/d        | 5              | 22.7      |
| Responsive to 800 mg/d | 2    | 40 (2/5)  |
| Resistance to 800 mg/d | 3  | 60 (3/5)  |
| Change to sunitinib | 3              | 13.5      |
| Change to erlotinib | 1             | 4.5       |
| Follow-up        |                |           |
| Dead            | 5              | 22.7      |
| Alive           | 17             | 77.3      |
| Adverse events  | 12             | 54.5      |
| No adverse events | 10            | 45.5      |
| Median follow-up time (mo) | 36   |           |
| Median treatment time (mo) | 15  |           |
| Median PFS (mo)  | 19             |           |

PFS = progression-free survival.
Following progression on 400 mg daily, 33% of GIST patients who crossed over to the higher dose achieved objective response rates and SD. This finding is consistent with that of the EORTC 62005 study, in which 133 (55%) patients who progressed on low-dose imatinib crossed over to high-dose imatinib; subsequently, 2% of patients had PR and 27% had SD. Similar to the imatinib therapy on GIST, 5 out of 22 patients exhibited secondary imatinib resistance for about 15 months of median treatment. According to the protocol for sunitinib therapy as the second line on GIST, sunitinib was also regard as the second line on DFSP in this study. As the dose of imatinib was increased from 400 to 800 mg, 40 percent (2/5) of cases achieved PR again, and the remaining 3 patients who switched to sunitinib therapy had a transient response. After developing resistance to sunitinib, 1 patient was administered with nilotinib but with no impact on disease control, the other 2 patients began imatinib therapy for the second time at the dose of 800 mg daily until death, and they exhibited transient response. Kamar et al present a case of recurrent and infiltrative DSFP where the imatinib treatment failed but impressive results were achieved after being administered with sorafenib, indicating that sorafenib could represent a therapeutic alternative after development of resistance to imatinib. Until now, the third lines of target therapy for DFSP are still unknown. To our knowledge, the DFSP patients swining to imatinib treatment for the second time may be one of the choices after imatinib and sunitinib resistance; however, the clinical use remains to be determined.

De Matteo et al showed that selected patients with metastatic GIST who have responsive disease or focal resistance to tyrosine kinase inhibitor therapy may benefit from elective surgical resection. In the present study, 1 patient with recurrent tumors in the buttock receiving resection for 15 times and occurring focal nodule resistance when treated with imatinib at 800 mg daily, underwent palliative debunking by surgical oncology. The patient maintained SD as long as 25 months after being administered with imatinib of 800 mg/d, and lives without signs of PD until the most recent follow-up. The optimal duration of treatment in patients who respond to imatinib is an unknown factor at this point. In the present study, the unresectable or metastatic patients who were responsive to imatinib therapy, if the patients tolerated imatinib very well, and issues of cost in view are out of concern, it is possible to continue the imatinib treatment as long as the rest of their lives or until the disease progressed. Further clinical trials will be necessary, however, to confirm the results reported here. The intent of neoadjuvant therapy should be to convert the unresectable tumor into a resectable tumor with negative margins or to limit the extent of reconstruction and comorbidities from excision. Ugurel et al showed that in 16 patients who received neoadjuvant imatinib, median tumor shrinkage was 31.5%, best overall response was 7.1% CR, 50.0% partial remission (PR), 35.7% SD, and 7.1% progressive disease (PD). In the present study, neoadjuvant treatment of imatinib from 1 to 6 months significantly reduced the preoperative lesion size in 4 out of 10 patients with unresectable DFSP, which resulted in a complete surgical excision. Especially 1 patient with metastatic lesion to sternum and mediastinum received complete surgical excision with precise histological margin after imatinib neoadjuvant treatment at a dose of 400 mg daily for 1 month (Figure 2A, B). Consistent with findings observed in 1 DFSP case with an unresectable pancreatic metastasis being treated in a neoadjuvant fashion with imatinib and an R0 resection was successfully performed. Our study documents that the utility of imatinib neoadjuvant therapy has the potential to transform patients with surgically challenging or recurrent tumors into better operative candidates, and the response observed in histologic findings following neoadjuvant imatinib may be useful in determining the best postoperative adjuvant therapy. In our study, all the patients, who received complete excision after imatinib neoadjuvant therapy always maintained adjuvant therapy for 1 year and until the recent follow-up, live with no signs of recurrent or distant metastases after stopping imatinib treatment.

Imatinib therapy was well tolerated with a safety profile in our small population similar to that observed in other solid tumor populations treated with that drug. In our study, although 12 out of 22 patients had side effects, which were minimal and did not lead to termination of therapy. However, there are some potential limitations for the retrospective nature of the study as follows: first, the small number of patients received imatinib therapy in this study for economical reasons. Second, we did not compare the OS and PFS between the metastatic patients who received imatinib therapy and those who did not. Third, some recurrent patients who were difficult to resection may be beneficial to imatinib treatment, but received resections without target therapy, with cosmetic defects or high morbidity. Further clinical trials will solve the potential limitation of the study.

In conclusion, imatinib in standard dosage allowed prompt and impressive clinical improvement, so that imatinib mesylate appears to be the therapy of choice in patients with metastatic or locally advanced disease not amenable to surgery. Neoadjuvant treatment of locally advanced and recurrent DFSP with imatinib improves surgical outcomes and may facilitate resection of difficult tumors; studies such as this may help to expand the indications of the US Food and Drug Administration for its use.

REFERENCES
1. McArthur GA, Deme GD, Fiore M, et al. Dermatofibrosarcoma protuberans treated at a single institution: a surgical disease with a high cure rate. J Clin Oncol. 2005;23:7669–7675.
2. Mendenhall WM, Zlotecki RA, Scarborough MT. Dermatofibrosarcoma protuberans. Cancer. 2004;101:2503–2508.
3. Simon MP, Navarro M, Roux D, et al. Structural and functional analysis of a chimeric protein COL1A1–PDGFB generated by the translocation t(17;22)(q22;q13.1) in dermatofibrosarcoma protuberans (DFP). Oncogene. 2001;20:2965–2975.
4. Shimizu A, O’Brien KP, Sjöblom T, et al. The dermatofibrosarcoma protuberans-associated collagen type Ialpha1/platelet-derived growth factor (PDGF) B-chain fusion gene generates a transforming protein that is processed to functional PDGFBB. Cancer Res. 1999;59:3719–3723.
5. Bichakjian CK, Olencki T, Alam M, et al. Dermatofibrosarcoma protuberans, version 1.2014. J Natl Compr Canc Netw. 2014;12:863–868.
6. Kimmel Z, Ratner D, Kim JYS, et al. Peripheral excision margins for dermatofibrosarcoma protuberans: a meta-analysis of spatial data. Ann Surg Oncol. 2007;14:2113–2120.
7. Serra-Guillem C1, Llombart B, Nagore E, et al. Mohs micrographic surgery in dermatofibrosarcoma protuberans allows tumour clearance with smaller margins and greater preservation of healthy tissue compared with conventional surgery: a study of 74 primary cases. Br J Dermatol. 2014doi: 10.1111/bjd.13417. [Epub ahead of print].
8. Rutgers EJ, Kroon BB, Albus-Lutter CE, et al. Dermatofibrosarcoma protuberans: treatment and prognosis. Eur J Surg Oncol. 1992;18:241–248.
9. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene. 2001;20:5054–5058.

10. Van Oosterom A, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protubersans treated with imatinib: imatinib target exploration consortium study B2225. J Clin Oncol. 2005;23:866–873.

11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–206.

12. Mentzel T, Beham A, Katenkamp D, et al. Fibrosarcomatous (“high-grade”) dermatofibrosarcoma protubersans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. Am J Surg Pathol. 1998;22:576–587.

13. Greco A, Roccati E, Miranda C, et al. Growth–inhibitory effect of STI571 on cells transformed by the COL1A/PDGFB rearrangement. Int J Cancer. 2001;92:354–360.

14. Gronchi A, Stacchiotti S, Pedentour F, et al. Response to imatinib mesylate (IM) in fibrosarcoma (FS) arising in dermatofibrosarcoma protubersans (DFSP). J Clin Oncol. 2008;abstract 10593.

15. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26:626–632.

16. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer. 2005;41:1751–1757.

17. Kamar FG, Kairouz VF, Sabri AN. Dermatofibrosarcoma protubersans (DFSP) successfully treated with sorafenib: case report. Clin Sarcoma Res. 2013;3:5.

18. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg. 2007;245:347–352.

19. Ugurel S, Mentzel T, Utkal J, et al. Neoadjuvant imatinib in advanced primary or locally recurrent dermatofibrosarcoma protubersans: a multicenter phase II DeCOG trial with long-term follow-up. Clin Cancer Res. 2014;20:499–510.

20. Dhir M, Crockett DG, Stevens TM, et al. Neoadjuvant treatment of dermatofibrosarcoma protubersans of pancreas with imatinib: case report and systematic review of literature. Clin Sarcoma Res. 2014;4:8.

21. Rutkowski P, Debiec-Rychter M, Nowecki Z, et al. Treatment of advanced dermatofibrosarcoma protubersans with imatinib mesylate with or without surgical resection. J Eur Acad Dermatol Venereol. 2011;25:264–270.