Advanced Dermatofibrosarcoma Protuberans Treatment With Imatinib: Experience From a Dedicated Sarcoma Medical Oncology Clinic in India

**INTRODUCTION**

Dermatofibrosarcoma protuberans (DFSP) is an exceedingly rare subtype of soft tissue sarcoma, constituting of 1% of all sarcomas. Behaviorally, DFSP rarely metastasizes (occurring in 5% of all cases), and the literature on metastatic DFSP remains conspicuously sparse. Histologically, DFSP can be classified as either classic or fibrosarcomatous (FS) variant. FS variant is characterized by more spindle cells, greater number of nuclei, and increased mitotic rate; unlike classic variant, immunohistochemically, CD34 expression is weak.

Elucidation of molecular mechanisms of DFSP has resulted in the development of targeted therapy directed toward platelet-derived growth factor β (PDGFβ) in advanced disease. Tumors of DFSP are characterized by pathologic chromosomal rearrangement that fuses the COL1A1 promoter gene of chromosome 17 to the PDGFβ gene of chromosome 22. Over-activation of PDGFβ receptor tyrosine kinase leads to cellular proliferation and tumor formation. Imatinib, a small molecular adenosine triphosphate analog, acts by competitively inhibiting the adenosine triphosphate–binding site of the PDGFβ receptor tyrosine kinase in DFSP and thus causing the downregulation of kinase activity leading to growth inhibition and apoptosis.

Although it has been known that treatment with imatinib has been used on this tumor, research publications about its use are limited, possibly because of the rarity of DFSP. After few case reports supporting the clinical use of imatinib, McArthur et al published the clinical and radiologic outcomes (Imatinib Target Exploration Consortium Study, B2225) in advanced DFSP (N = 10; locally advanced, n = 8; metastatic, n = 2) using imatinib 800 mg per day and found a response rate of 90%. The largest group of prospective data for advanced DFSP came from the pooled analysis of two distinct phase II trials conducted by the European Organisation...
for Research and Treatment of Cancer (EORTC) and SWOG groups, consisting of 24 patients with locally advanced and metastatic DFSP receiving doses of imatinib ranging from 400 and 800 mg, respectively. The objective response rate was 46%, and median time to progression was 1.7 years. There was no difference between the different doses of imatinib in terms of overall response rates and progression-free survival (PFS). Recently, Rutkowski et al analyzed 31 patients with locally advanced/metastatic DFSP treated with imatinib for long-term outcomes and prognostic factors. Presence of metastatic disease and FS variant were associated with worst prognosis. Here, we report the experience of consecutive patients with metastatic/unresectable DFSP presenting in the last 2 years to our sarcoma medical oncology clinic.

MATERIALS AND METHODS

This is a retrospective study evaluating patients with locally advanced/metastatic DFSP who were registered in a sarcoma medical oncology clinic between January 2016 and July 2017, and followed up until November 2017. The pathology of all the cases was reviewed by a sarcoma pathologist, and all cases were reviewed in a multidisciplinary clinic.

The dose of imatinib used in the clinic depended on the physician’s discretion and the response and tolerance of the patient. Data were studied through hospital records, including the age, sex, site, metastatic lesions, histopathology, dose of imatinib, response rate, and outcomes. The statistical analysis was done through SPSS 23 (SPSS, Chicago, IL). Nominal data are provided as number (%) and continuous data as median (range). PFS was calculated from the date of random assignment to the first date of documented progressive disease or the date of death from any cause.

RESULTS

A total of seven patients with the diagnosis of metastatic (n = 6) or locally advanced (n = 1) DFSP were referred to the sarcoma medical oncology clinic during this time. Median age of the patients was 35 years (age range, 19 to 54 years). The majority of the patients were men (n = 6; 85.7%). The locations of the primary lesion are listed in Table 1 (one forehead and eyelid; one nape of neck; five trunk). The median time from baseline diagnosis to development of metastasis/unresectability was 42 months (range, 24 to 120 months). Of seven patients at the time of presentation to our clinic, six patients had FS transformation and one patient had classic DFSP (Fig 1). Patient characteristics are summarized in Table 1. Best response was partial response in five patients (responses for patients 1 and 7 are shown in Figs 2 and 3, respectively), stable disease in one patient, and progressive disease in one patient. Table 2 lists treatment characteristics, including dose of imatinib, response, and current status. Of all patients with metastatic disease (n = 6), the most common site of metastasis was the lung (83%), followed by soft tissue (66.6%) and bones (33%). The median number of metastatic sites was three (range, one to five), suggesting high burden of disease. Of those patients who started chemotherapy, four patients have experienced progression to date (Table 3). Median PFS in our patients was 14 months (Fig 4). One patient was lost to follow-up, and the rest were followed until the last date of follow-up.

### Table 1. Clinical Details of Patients With DFSP

| Patient | Age (years) | Sex | Variant | Site of Disease | Metastatic v Locally Advanced |
|---------|-------------|-----|---------|----------------|-----------------------------|
| 1       | 33          | Male| DFSP    | Forehead       | Locally advanced            |
| 2       | 54          | Male| DFSP with FS transformation | Shoulder       | Metastatic                   |
| 3       | 48          | Male| DFSP with FS transformation | Trunk          | Metastatic                   |
| 4       | 35          | Male| DFSP with FS transformation | Abdomen and trunk | Metastatic                   |
| 5       | 36          | Male| DFSP with FS transformation | Trunk          | Metastatic                   |
| 6       | 19          | Male| DFSP with FS transformation | Trunk          | Metastatic                   |
| 7       | 35          | Female| DFSP with FS transformation | Nape of neck  | Metastatic                   |

Abbreviations: DFSP, dermatofibrosarcoma protuberans; FS, fibrosarcomatous.


**Fig 1.** (A) Uniform population of spindled tumor cells arranged in a distinct, monotonous, storiform pattern around an inconspicuous vasculature. There is minimal nuclear pleomorphism and only low mitotic activity. (B) Immunohistochemistry performed for CD34 showing diffuse immunopositivity in the tumor cells. (C) Fibrosarcomatous dermatofibrosarcoma protubersans, where the tumor cells are arranged in fascicular architecture and herringbone pattern (loss of storiform pattern), with moderate nuclear pleomorphism and increased mitotic activity. (D) Immunohistochemistry performed for CD34 showing loss of CD34 immunostaining in a case of fibrosarcomatous transformation. H&E, hematoxylin and eosin.

**DISCUSSION**

The role of imatinib is well established in chronic myeloid leukemia and GI tumors. The data regarding the outcome of advanced DFSP treated with imatinib are sparse, and in the developing world they are limited to occasional case reports only. This could be because of a lack of expert histopathology, lack of translocation testing, and absence of dedicated sarcoma clinics and multidisciplinary teams. This is the...
first series from India with consecutive patients with advanced DFSP from the sarcoma medical oncology unit of a tertiary care institute.

Our patients presented a decade earlier than the SWOG/EORTC pooled analysis data and B2225 study, and this could be attributed to the younger population structure of Indian patients. There was male predominance in our series, as has been shown in the previous SWOG/EORTC pooled analysis. However, in the study by McArthur et al (B2225 study), there was an equal number of male and female patients. The time from baseline diagnosis to metastasis/unresectability was 42 months, which was 34 months in the SWOG/EORTC pooled analysis. The trunk was the most common primary site, followed by the head and neck, similar to the SWOG/EORTC pooled analysis; in the B2225 study, the head and neck was the most common site (30%). We had six out of seven (85.7%) patients with FS transformation, in contrast to the other studies where the FS variant was 43% to 52%. The response rate in our series was 71%. Response

| Patient | Surgery Done Up Front | Radiation Treatment and Line of Radiation | Dose of Imatinib (mg) | Best Response | Duration of Imatinib | Current Status |
|---------|-----------------------|------------------------------------------|----------------------|---------------|---------------------|----------------|
| 1       | Done in nononcological setup outside our institute | No radiation given after surgeries | 400 | PR | 5 months | Response persisting |
| 2       | Surgery done outside oncological setup | RT was given up front | 400 | PR | 5 months | Progressed after 5 months |
| 3       | Upfront surgery done in our institute; margins positive | Surgery was given up front and in third recurrence | 400 | PD | 3 weeks | Lesions progressed rapidly (superficial lesions) |
| 4       | Adequate surgery done | Yes, up front | 600 | PR | 13 months | Progressed after 13 months |
| 5       | Upfront surgery done in nononcological setup | No RT given after surgeries | 800 | PR | 20 months | Response persisting |
| 6       | Surgery with close margin | RT given at third recurrence | 800 | SD | 16 months | Progressed after 16 months of imatinib |
| 7       | Adequate surgery done | No RT given | 400 | PR | 5 months | Response persisting |

Abbreviations: PD, progressive disease; PR, partial response; RT, radiation therapy; SD, stable disease (following mRECIST 1.1 criteria).
rates in various studies have been shown to be between 46% and 90%, with FS variant having the shortest lasting responses.8-10 PFS has varied in the literature in different studies. For example, in the pooled analysis by SWOG/EORTC, 1-year PFS was 57.18%, whereas in another retrospective analysis the 5-year PFS was 58%, although the percentage of FS variant and patients with metastatic disease was almost the same in both studies.9,10 Shorter PFS of 14 months in our study could be explained by the predominance of FS variant and metastatic disease along with high disease burden.

Limitations of this study are that it was a small, retrospective study with limited follow-up, which is frequently the case with rare tumors. We have not done mutation testing in our cohort, but we believe that partial response/stable disease while receiving imatinib reinforces the diagnosis in the setting of a tertiary care bone and soft tissue–specific pathologist. This is the first case series to our knowledge from the developing world solely on the basis of the histopathology, and the results are encouraging. Until we have molecular techniques available, good histopathology reporting and multidisciplinary management can be the cornerstone of the treatment of this rare disease.

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**Table 3.** Post-Treatment Plan and Outcomes

| Patient | Postimatinib Treatment Plan and Outcomes |
|---------|----------------------------------------|
| 1       | Planned for metastatectomy in orbit and scalp |
| 2       | After disease progression, patient was given pazopanib for 2 months and disease progressed. Currently planned for doxorubicin chemotherapy |
| 3       | After disease progression on imatinib, patient was given doxorubicin for one cycle and had disease progression after that cycle. |
| 4       | After disease progression on imatinib, patient was given five cycles of doxorubicin and has stable disease until that time. |
| 5       | Response on imatinib persisting until last follow-up |
| 6       | Patient was started on pazopanib 800 mg once a day and has stable disease for last 1 year 3 months |
| 7       | Response on imatinib persisting until last follow-up |

Fig 4. Progression-free survival in months.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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