Dermatofibrosarcoma Protuberans (DFSP):
An Update on Molecularly Targeted Therapy of Advanced Cases
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This article is also available at:
http://sarcomahelp.org/learning_center/dfsp_targeted.html

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INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare dermal tumor (comprising approximately 1% of soft tissue sarcomas) with typically indolent growth over years and a probability of regional/distant metastases of less than 2-3%.1,2 The disease most commonly affects adults aged 20-50 years. The estimated incidence of DFSP is 3 to 4.2 cases per million people per year, with equal sexual distribution.3,4 In DFSP harboring areas of high-grade fibrosarcoma (called fibrosarcomatous DFSP or DFSP-FS) metastases develop in the range of 8-15%,5,7 which is evidence of its more aggressive behavior. Distant metastases are usually localized in the lungs and less commonly in the lymph nodes. The standard treatment of this cutaneous sarcoma is radical, wide local excision; however a high rate of local control is also reported with the application of Mohs micrographic surgery.9 Since achieving negative margins is critical to prevent local relapse, the recommended margin of surgical excision is usually above 2 cm.1 Radical surgery often requires the use of reconstructive techniques and may result in cosmetic disfigurement or functional impairment. Such mutilating procedures might be avoided if appropriate Mohs micrographic surgery can be applied.9 If radical resection is not feasible, radiotherapy may be applied to reduce the risk of local recurrence. The dose of radiotherapy varies within the range of 50-70 Gy.10 Overall, local recurrences have been reported in the range of 24-90%.1,11

Molecular Biology

Almost all cases of DFSP are characterized by the distinctive reciprocal rearrangement of chromosomes 17 and 22 in the form of translocation t(17;22)(q22;q13) and often a supernumerary ring chromosome.12-16 This rearrangement results in the fusion of collagen type
I α1 chain gene (COL1A1) to the platelet-derived growth factor (PDGF) B-chain gene (PDGFB). This COL1A1-PDGFB fusion may be identified in virtually all DFSP cases by sensitive molecular diagnostic tests: the fluorescence in-situ (FISH) method or multiplex reverse transcription polymerase chain reaction (RT-PCR), which is extremely important for differential diagnosis of atypical, metastatic DFSP or DFSP-FS.17,18 The consequences of these molecular events include the deregulation of PDGFB chain expression, the unscheduled expression of COL1A1/PDGFB fusion protein processing to mature homodimer PDGF-BB, and the continuous autocrine activation of PDGFR receptor B (PDGFRB), which is protein tyrosine kinase acting as a potent growth factor.19-21 The rearranged PDGF gene leads to the production of functional platelet-derived growth factor that can bind to and activate platelet-derived growth factor receptors on tumor cells, providing an autocrine and/or paracrine mitogenic stimulus, leading to malignant transformation.22 In some cases of DFSP with no evidence of the 17;22 chromosomal translocation, other molecular abnormalities were shown, such as t(5;8).23

**Fluorescence in situ hybridization (FISH)** is a laboratory technique used to detect a specific segment of DNA and its copies in a cell. The method can also identify structurally abnormal chromosomes. Specific segment of DNA is chemically modified and labeled in the laboratory so that it will become fluorescent under a special microscope. This DNA serves as a probe that can find matching segments of DNA.

**Reverse transcription polymerase chain reaction (RT-PCR)** is a variant of PCR in which an RNA strand is first reverse transcribed into complementary DNA sequence (cDNA). Obtained cDNA is then amplified in a typical polymerase chain reaction.

**CLINICAL RESULTS**
Advances in the understanding of the molecular mechanisms of DFSP have resulted in the introduction of targeted therapy acting on PDGFR to clinical practice. Imatinib mesylate is a tyrosine kinase inhibitor specifically directed toward BCR/ABL, KIT, FMS (the receptor for Colony Stimulating Factor 1), ARG (ABL-related gene) and PDGFR alpha and beta. It is an effective systemic therapy in most cases of DFSP. Imatinib competes with the adenosine triphosphate (ATP) molecule, blocking the tyrosine kinase receptor's ability for autophosphorylation, which results in inhibition of the damaged pathway of signal transduction and restoration of proper intracellular signaling.

**Imatinib**: A small molecule inhibitor that targets several tyrosine kinases including the Abelson leukemia (ABL) kinase, KIT, PDGFR, ARG and FMS. It is used to treat patients with chronic myelogenous leukemia, gastrointestinal stromal tumors and myeloproliferative diseases with translocations involving PRGFR genes. Imatinib mesylate (Glivec®) is administered orally and the dose of 400-800 mg daily is recommended.

The observation that autocrine overproduction of PDGFB from gene rearrangement is a key pathogenetic factor19,20 and provoked the *in vitro* research, which showed inhibition of DFSP cell growth after exposure to imatinib mesylate.22,24 The further demonstration of the inhibitory effect of imatinib on six different DFSP cell lines *in vitro* and *in vivo*35 led to the investigation of this new therapeutic approach in the clinic. The first reports on six patients suggested the usefulness of imatinib in metastatic and locally advanced DFSP.28-31 The next series of ten patients with locally advanced and/or metastatic DFSP treated in the Imatinib Target Exploration Consortium Study B2225 showed 100% response rate (50% were complete responses) in locally advanced cases and one partial response lasting seven months in the metastatic setting.32 These observations resulted in imatinib’s registration as the therapy of choice in inoperable and/or metastatic DFSP. In a phase II trial33 evaluating the activity of imatinib in life-threatening malignancies expressing imatinib-sensitive tyrosine kinase, DFSP was the only one out of five tumor types where notable
activity was shown with extensive regression in ten of twelve cases (50% partial remissions, 33.3% complete remissions).

Combined analysis of two prematurely closed phase II, single arm, open-label trials (European Organisation for Research and Treatment of Cancer no. 62027 and the Southwest Oncology Group no. S0345) regarding the efficacy of imatinib in advanced (inoperable and/or metastatic) DFSP has demonstrated a clinical benefit rate exceeding 70% for twenty-five patients with advanced DFSP, with median time to progression of 1.7 years. Another study on fifteen patients who did not qualify for clinical trials has proven the striking activity of imatinib mesylate in advanced DFSP, with clinical benefit rate approaching 80% as well as median Progression Free Survival (PFS) and Overall Survival (OS) were not reached. It has been shown that DFSP-FS is also sensitive to imatinib, although responses seem to be shorter in duration. DFSP-FS tumors lacking the 17;22 chromosomal translocation do not respond to imatinib. The presence of a molecular target (COL1A1-PDGFB) is obligatory to confirm diagnosis of DFSP in every case prior to the start of imatinib therapy.

**Clinical Benefit Rate**: a statistical parameter defined as a sum of complete responses, partial responses and stable disease observed in a clinical trial.

Given the fact that complete, wide surgical excision is the standard treatment in localized resectable DFSP cases, neoadjuvant imatinib therapy leading to tumor downstaging and less cosmetic disfigurement, functional impairment and excision morbidity appears very attractive. Lebbe et al. presented a preliminary report on twenty-five resectable DFSP (median size – 4.5 cm) treated in a phase II trial with preoperative imatinib at the dose of 600 mg. daily. Objective partial response according to RECIST was observed in nine cases (36%). Present results indicate that some DFSP cases initially evaluated as unresectable/metastatic or necessitating disfiguring surgery were evaluated as resectable after imatinib therapy. This rational approach leading to complete remission may be potentially curative, although longer follow-up is needed. Further studies are necessary for elucidating whether preoperative imatinib therapy reduces the need for wide surgical margins or whether imatinib has activity as adjuvant therapy in cases of positive margins after excision or in other high-risk patients.

The dose of imatinib used in mentioned studies ranged from 400 to 800 mg. daily. Available clinical data are not sufficient to determine the optimal dose of initial imatinib treatment, since objective responses were observed both with lower and higher dosing schedules. The majority of patients treated with imatinib experience side effects during treatment, but almost all are mild and manageable; the most common being fluid retention/edema, anemia, fatigue, nausea, skin rash, thrombocytopenia, vomiting, neutropenia and diarrhea.
FUTURE DIRECTIONS
There is still uncertainty concerning the mechanisms of imatinib action and resistance in the treatment of DFSP, as well as a need to identify novel molecular markers that predict response to such therapy. It was presumed that imatinib’s effect resulted from the inhibition of phosphorylation of PDGFR. Unexpectedly, the clinical activity of imatinib is striking even in DFSP that expresses a relatively low amount of activated PDGFRB. If tumor cells are dependent on that signaling mechanism, it seems that the inhibition of low-level receptor tyrosine kinases may still be clinically effective.

SUMMARY
Imatinib is currently the gold standard therapy of inoperable, metastatic, or recurrent cases of DFSP. Such treatment may potentially facilitate resection or decrease disfigurement related to an extensive surgical procedure. A significant percentage of patients may be rendered free of disease by excision of residual disease following partial response on imatinib. Current therapy of DFSP with the 17;22 chromosomal translocation should be definitively conducted by a multidisciplinary team, including an oncological surgeon. The use of imatinib mesylate as initial therapy to decrease the extent of wide surgical resection and related morbidity should be always considered.

REFERENCES


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