NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 2• 165–168

The partial response of lung metastases arising from *dermatofibrosarcoma protuberans* after one month of imatinib mesylate therapy – a case report

Włodzimierz Ruka[1], Sławomir Falkowski[1], Urszula Grzesiakowska[2], Justyna Wudarska[2], Anna Nasierowska-Guttmejer[3], Anna Nowak-Dement[1], Zbigniew Nowecki[1], Konrad Ptaszyński[3], Piotr Rutkowski[1]

We report the case of a 36 year old woman with multiple reccurent dermatofibrosarcoma lung metastases, who was primary treated surgically (multiple metastases resection) and with different chemotherapy regimens, who finally demonstrated progressive unresectable disease. The patient was experimentally treated with tyrosine kinase inhibitor imatinib mesylate (400 mg once daily). After one month of treatment the patient demonstrates partial regression (PR) of lung metastases according to RECIST criteria (total tumor dimensions decreased by over 30%). This case demonstrates the activity of a new small molecule inhibitor – imatinib mesylate – in the treatment of metatastatic dermatofibrosarcoma, probably by the inhibition of the platelet-derived growth factor β (PDGFβ) receptor.

Częściowa regresja przerzutów do płuc u chorej na *dermatofibrosarcoma protuberans* po miesiącu leczenia imatinibem mesylate – opis przypadku

W pracy przedstawiono przypadek 36 letniej chorej na dermatofibrosarcoma z przerzutami do płuc leczonej kilkukrotnymi resekcjami, różnymi schematami chemioterapii i u której ostatecznie stwierdzono nieoperacyjne przerzuty do płuc z cechami progresji nie dającej się opanować leczeniem przeciwnowotworowym. U chorej rozpoczęto leczenie inhibitorem kinazy tyrozynowej – imatinibem w dawce 400 mg 1 raz dziennie. Po miesiącu leczenia stwierdzono częściową remisję (PR) zmian przerzutowych w płucach ocenioną zgodnie z kryteriami RECIST (zmniejszenie sumy najdłuższych wymiarów zmian o więcej niż 30%). Prezentowany przypadek wskazuje na aktywność nowego leku przeciwnowotworowego – imatinibu w leczeniu przerzutowego dermatofibrosarcoma, prawdopodobnie w mechanizmie blokowania receptora dla płytkowopochodnego czynnika wzrostu β (PDGFRβ).

Key words: *dermatofibrosarcoma protuberans*, imatinib, *sarcoma*
Słowa kluczowe: *dermatofibrosarcoma protuberans*, imatinib, mięsak

Introduction

Dermatofibrosarcoma protruberans (DP) is a rare, low – grade sarcoma infiltrating the skin, with aggressive local growth and high local recurrence potential. Wide surgical excision of the tumor is the best method of treatment. A small percentage of patients (approximately <5%) may develop metastatic disease, mainly to the lungs, lymph nodes and bones. In the case of dissemination, the prognosis of the majority of patients is almost always fatal and similar to the other soft tissue sarcomas, although the progression is usually slow and lasting several years [1-5]. In metastatic disease there are not any established, standard treatment modalities.

Imatinib mesylate is a new-generation antineoplastic agent with tyrosin-kinase inhibitor activity. Imatinib has been shown to have impressive efficiency in CML (chronic myeloid leukemia) and GIST (gastrointestinal stromal tumor) treatment, targeting Bcr-Abl and c-KIT receptors, respectively. Imatinib *in vivo* has also shown activity against PDGF-driven tumor models including glioblastoma, DP (dermatofibrosarcoma protuberans) and chronic myelomonocytic leukemia [6, 7].

Till now three cases of patients with advanced DP treated with imatinib mesylate have been published, with satisfactory results reported in two of them [8, 9]. The aim of our report is to present partial response of lung metastases during imatinib mesylate therapy in a patient with DP.

[1] Soft Tissue/Bone Sarcoma and Melanoma Department
[2] Department of Radiology
[3] Department of Pathology
The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Patient and methods

A Thirty year old (b. 1966) female patient was seen first time at the Department of Soft Tissue/Bone Sarcoma and Melanoma in November 1996. She was referred because of lung metastases which were found accidentally on a chest X-ray performed 3 years after primary tumor excision.

The excision of the primary tumor located in the left subscapular region was performed under local aneaesthesia in a county hospital outpatient clinic in October 1993. The postoperative pathology report revealed dermatofibrosarcoma protuberans (DP). The diagnosis was confirmed by two independent pathologists. Over a year later she was re-operated on because of local recurrence in the subcutaneous part of the scar and subsequently, second pathologic examination confirmed the diagnosis of dermatofibrosarcoma. However, at that time, fibrosarcomatous areas were found within the specimen. On this basis the surgeon decided to extend the excision and to use the thin skin graft to cover the ample tissue defect. 18 months later, without any clinical symptoms, lung metastases were detected on accidentally performed chest radiograms. On first admission to our Department in November 1996, additional diagnostic investigations did not disclose any other abnormalities, except lung metastases. Ifosfamide in monotherapy was decided on and introduced as systemic treatment. During the next 5 years, i.e. from November 1996 to June 2001, the patient was treated by three different chemotherapy regimens and underwent three subsequent thoracotomies because of recurrent lung metastases. The treatment details are shown in Table I. Histologic findings after each thoracotomy demonstrated the presence of lung metastases with viable sarcoma cells and the diagnosis of metastatic dermatofibrosarcoma was confirmed. In last exam (i.e. after third thoracotomy performed in February 2001), immunohistochemical staining was positive for CD34 and negative for CD117. Unfortunately, after the next fifteen months of follow-up fourth recurrence (two bilateral lung metastatic lesions) was revealed. The patient did not undergo subsequent thoracotomy because her lung function tests (FVC – forced vital capacity and FEV_1 – forced expiratory volume in one second) were on bordeline values. Palliative care and the best supportive treatment (cyclophosphamide, etoposide, ketoprofen, ranitidine, allopurinol) were introduced. The evident progression of lung metastases was noted at the end of October 2002.

The repeated pathology examination of paraffin-embedded tissue from metastasis removed during last thoracotomy (in February, 2001) has confirmed immunohistochemical staining positive for CD34 and negative for CD117.

Taking into account her young age, WHO performance status "0" and based on data from literature she was offered to be treated with imatinib mesylate (Glivec®), Gleevec™) [8, 9]. It was decided to start therapy with 400 mg per day orally with the possibility of dose enlargement, if necessary, up to 800 mg daily (400 mg twice daily). Informed consent was obtained.

For assessment of the objective response to the treatment, the longest diameters of both lung metastases measured on plain chest X-ray, were chosen. In the meantime, supportive treatment was ceased at the beginning of November 2002 to maintain at least a 30 day treatment-free interval before introducing imatinib.

Results

At first measurable features of progression in the last several weeks before imatinib therapy introduction were calculated. During the three weeks of follow-up both pulmonary metastatic lesions were evidently enlarged; the right metastatic nodule from 42 mm to 51 mm (21%, 9/42mm) and the left supraphrenic tumor from 25 to 27 mm (8%, 2/25) (Table II, Figure 1A and 1B). Altogether the features of progression could be expressed as 16% (11/67).

Table II. Results of measurements of metastatic lung metastases

date	right nodule	left nodule	total	comment
25/11/02	42 mm	25 mm	67 mm	
18/12/02*	51 mm	27 mm	78 mm	progression
20/01/03	35 mm	17 mm	52 mm	partial response

*) – first day of therapy with imatinib 400 mg daily

Imatinib therapy was introduced on December 18, 2002. After 31 days of treatment the largest diameter of bigger nodule decreased to 35 mm, (i.e. by 31% of

Table I. Summary of treatment decision details

date	event	comments
10/1993	local excision	first operation of DP located in left subscapular region
01/1995	re-excision	second operation for local recurrence
02/1995	re-excision	third operation – wider excision of scar with thin skin graft
09/1996	chest X-ray, CT	lung metastases
11/1996	chemotherapy	ifosfamide, partial response (PR)
08/1997	sternotomy	bilateral metastasectomy (two tumors)
06-10/1998	chest X-ray, CT	new lung metastases with slow progression during follow-up
11/1998	chemotherapy	doxorubicin, dacarbazine, four courses, partial response
03/1999	right thoracotomy	metastasectomy (three tumors)
03-06/1999	chemotherapy	doxorubicin, dacarbazine, four courses postoperatively
08-10/2000	chest X-ray, CT	the third recurrence of metastasis, right lung solitary with slow progression during follow-up
11/2000	chemotherapy	doxorubicin, cis-platin; vepesid cis-platin, stable disease
02/2001	right re-thoracotomy	metastasectomy (one tumor)
03-06/2001	chemotherapy	vepesid, cis-platin, six courses postoperatively
05/2002	chest X-ray	the fourth recurrence, bilateral lung metastases
06-11/2002	chest X-rays	paliative therapy, slow progression of lung metastases
18/12/2002	chemotherapy	imatinib mesylate 400 mg p.o. daily
20/01/2003	chest X-ray	partial response (PR)

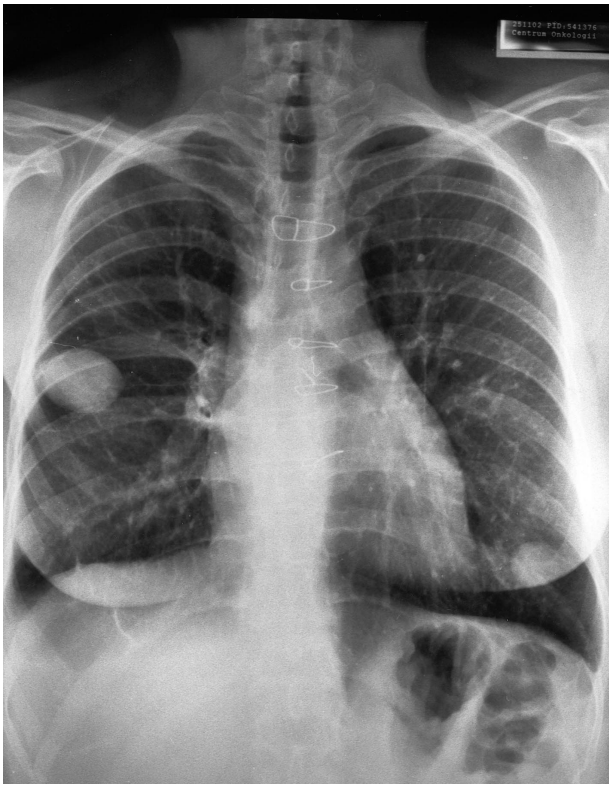

Figure 1A

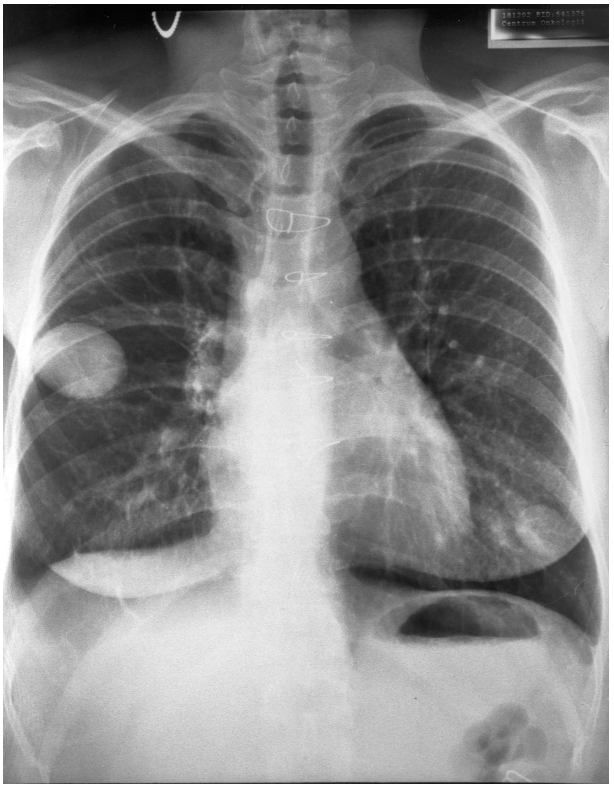

Figure 1B

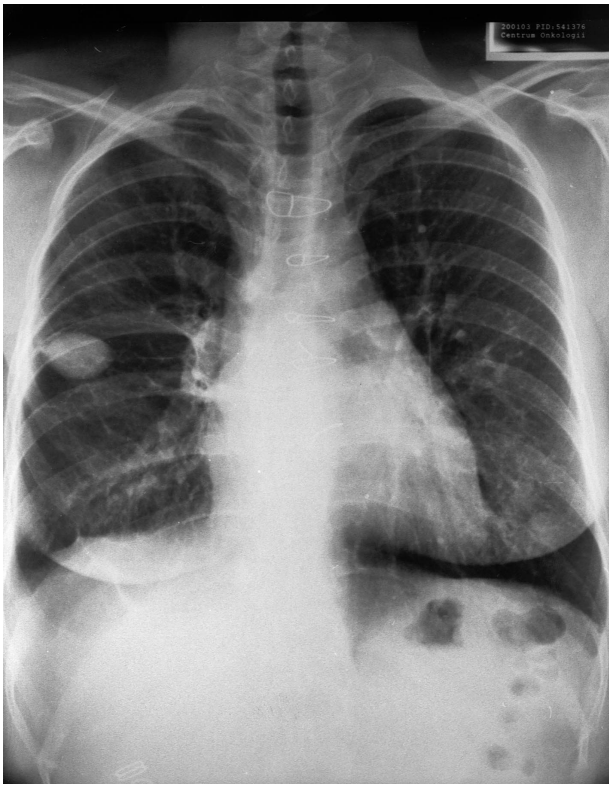

Figure 1C

Figure 1 – Plain chest X-rays
A – Three weeks before treatment start – on 25 November, 2002
B – At the day of treatment beginning – on 18 December, 2002
C – One month after imatinib therapy – on 20 January, 2003

previous size), and the longest diameter of the smaller lesion decreased to 17 mm (corresponding to a 37% response) (Figure 1B and 1C). The summed up diameters of both target lesions decreased to 52 mm i.e. a 33% reduction of baseline diameter (Table II). No new lesions were observed (Figure 1C). According to RECIST criteria it could be defined as the partial response (PR).

No toxicity nor other significant adverse events of imatinib therapy were observed.

Discussion

Imatinib mesylate is an inhibitor of tyrosine kinases including Bcr-Abl (responsible for CML), c-KIT (responsible for GIST) and PDGFβ receptors. The mechanism of the reduction of metastases in our patient is unclear. Inhibition through the Kit signaling pathway is questionable, because CD117 (for c-KIT cell surface receptor) immunohistochemistry examination was negative. Alternatively, the treatment effect of imatinib might be due to another target connected with the PDGFβ receptor. It has been determined that DP cells in culture show greater response to PDGF(BB) than normal fibroblasts, as well as showing an upregulation of PDGFβ receptor revealed by binding assay and immunoblotting analysis. This suggests that blocking the overexpression of the PDGFβ receptor might play a role in the inhibition of progression of DP lung metastases in this patient [10]. Imatinib probably has also antiangiogenic activity. The inhibition of PDGF-, VEGF- and bFGF-stimulated vascularization of mouse subcutaneous implants by

imatinib was shown on *in vitro* and *in vivo* models of assays for growth factor-induced angiogenesis. These results suggest, that imatinib *in vivo* may inhibit not only endothelial cell activation (by VEGF and bFGF) but smooth muscle cells or pericytes, as well. This could prevent the stabilization both of tumor capillaries and bigger vessels in the tumor [6].

It is worth mentioning that the other DP-like family of tumors, apart from classic dermatofibrosarcoma protuberans, includes: giant cell fibroblastoma (juvenile analogue of DP), Bednar tumor (pigmented variant of DP) and possibly, superficial adult fibrosarcoma (equivalent of fibrosarcomatous transformation of DP). The common feature of all these tumors is the expression of the COL1A1-PDGFB chimeric gene resulting from a reciprocal translocation, t(17;22), and/or (in adults) supernumerary ring chromosome, r(17:22). What is more interesting, the fibrosarcomatous areas of primary and metastatic tumors may maintain positive immunohistochemistry staining for CD34 [1, 11-18].

Because of the uncertain effect of imatinib therapy in dermatofibrosarcoma, we decided to choose a treatment regimen proposed in the protocol of EORTC 62005 trial for GIST treatment: the basic imatinib dose of 400 mg daily and, if not effective, increase drug dose up to 800 mg daily. In this case, a partial response was achieved after 400 mg daily of imatinib dosage. The case report is the first Polish patient description of impressive response of metastatic dermatofibrosarcoma to imatinib mesylate therapy.

Włodzimierz Ruka MD, PhD
Soft Tissue/Bone Sarcoma and Melanoma Department
The Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology, Warsaw, Poland
e-mail: ruka@coi.waw.pl

References

1. Ohtani N, Fukusato T, Tezuka F. Sarcomatous dermatofibrosarcoma protuberans metastasized to the lung: preservation of CD34 expresion in tumor cells. *Pathol Int* 1998; 48: 989-93.
2. Grosdidier G, Sibille P, Borrelly et al. Pulmonary metastasis of a dermatofibrosarcoma. *Ann Chir* 1991; 45: 724-5.
3. Volpe R, Carbone A. Dermatofibrosarcoma protuberans metastatic to lymph nodes and showing a dominant histiocytic component. *Am J Dermatopathol* 1983; 5; 327-34.
4. Hausner RJ, Vargas-Cortes F, Alexander RW. Dermatofibrosarcoma protuberans with lymph node involvement. A case report of simultaneous occurrence with an atypical fibroxanthoma of the skin. *Arch Dermatol* 1978; 114; 88-91.
5. Kahn LB, Saxe N, Gordon W. Dermatofibrosarcoma protuberans with lymph node and pulmonary metastases. *Arch Dermatol* 1978; 114; 599-601.
6. Buchdunger E, O'Reilly T, Wood J. Pharmacology of imatinib (STI571). *Eur J Canc* 2002; 38: suppl. 5 28-36.
7. Sjoblom T et al. Growth inhibition of dermatofibrosarcoma protuberans tumors by the platelet-derived growth factor receptor antagonist STI571 through induction of apoptosis. *Cancer Res*. 2001, 61, 5778-5783.
8. Awan RA. Patients with metastatic sarcoma arising from dermatofibrosarcoma protuberans (DFSP) may respond to imatinib (STI571, Gleevec). *ASCO Conference*, Orlando, 2002, abstract 1637.
9. Rubin BP et al. Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. *JCO* 2002; 20: 3586-91.
10. Kikuchi K, Soma Y, Fujimoto M et al. Dermatofibrosarcoma protuberans: increased growth response to platelet-derived factor BB in cell culture. *Biochem Biophys Res Commun* 1993; 196: 409-15.
11. Sheng WQ, Hashimoto H, Okamoto S et al. Expresion of COL1A1-PDGFB fusion transcripts in superficial adult fibrosarcoma suggests a close relantionship to dermatofibrosarcoma protuberans. *J Pathol* 2001; 194: 88-94.
12. Maire G, Martin L, Michalak-Provost S et al. Fusion of COL1A1 exon 29 with PDGFB exon 2 in a der(22)t(17;22) in a pediatric giant cell fibroblastoma with a pigmented Bednar tumor component. Evidence for age-related chromosomal pattern in dermatofibrosarcoma protuberans and related tumors. *Cancer Genet Cytogenet* 2002; 134: 156-61.
13. Nishio J, Iwasaki H, Ishiguro M et al. Supernumerary ring chromosome in a Bednar tumor (pigmented dermatofibrosarcoma protuberans) is composed of interspersed sequence from chromosomes 17 and 22: a fluorescence in situ hybridization and comparative genomic hybridization analysis. *Genes Chromosomes Cancer* 2001; 30: 305-9.
14. Mentzel T, Beham A, Katenkamp D et al. Fibrosarcomatous ("high grade") dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. *Am J Surg Pathol* 1998; 22: 576-87.
15. Ding J, Hashimoto H, Enjoji M. Dermatofibrosarcoma protuberans with fibrosarcomatous areas. A clinicopathologic study of nine cases and a comparison with allied tumors. *Cancer* 1989; 64: 721-29.
16. Zamecnik M. Fibrosarcomatous dermatofibrosarcoma protuberans with giant rosettes. *Am J Dermathopathol* 2001; 23: 41-5.
17. Goldblum JR. CD34 positivity in fibrosarcomas which arise in dermatofibrosarcoma protuberans. *Arch Pathol Lab Med* 1995; 119: 238-41.
18. Pedeutour F, Simon MP, Minoletti F et al. Translocation, t917;22)(q22;q13), in dermatofibrosarcoma protuberans: a new tumor-associated chromosome rearrangement. *Cytogenet Cell Genet* 1996; 72: 171-4.

Paper received: 30 January 2003
Accepted: 15 Febrary 2003