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Original Article

Sunitinib for patients with locally advanced or distantly metastatic dermatofibrosarcoma protuberans but resistant to imatinib

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Abstract: Purpose: This study evaluated the efficacy and adverse effects of Imatinib therapy to advanced Dermatofibrosarcoma protuberans (DFSP) and Sunitinib therapy to advanced Dermatofibrosarcoma protuberans (DFSP) after Imatinib resistance. Methods: We analyzed the efficacy, adverse effects and survival of 95 patients with locally advanced or metastatic DFSP treated by Imatinib between January 2003 and December 2009, and also analyzed the efficacy and adverse effects of 30 patients after Imatinib failure between January 2008 and December 2011. Results: In all 95 patients treated by Imatinib, 16 had complete response (CR, 16.8%), 44 had partial response (PR, 46.3%), 23 had stable disease (SD, 24.2%) and 12 had progressive disease (PD, 12.6%). The DCR (CR+PR+SD) was 87.4%. The median PFS was 23 months and the OS was 40 months. For 30 patients had Sunitinib treatment after Imatinib failure, 2 had CR (6.7%), 10 had PR (33.3%), 12 had SD (40%) and 6 had PD (20%). The disease control rate (DCR=CR+PR+SD) was 73.3%. The progression free survival (PFS) of CR and PR patients were 22 months and 20 months respectively. The PFS of 12 SD was 18 months, and overall survival (OS) was 28 months. And the median PFS and OS of all 30 patients were 19 and 27 months respectively after Sunitinib treatment. Most of the Imatinib-induced adverse effects are of grade 1-2, including nausea, water retention/edema, fatigue, etc. Conclusion: Imatinib has been proven to be effective and well-tolerated in the treatment of locally advanced or inoperable patients with DFSP. After Imatinib failure, Sunitinib therapy showed good clinical efficacy and tolerated adverse effects as a new treatment option for such patients.

Keywords: Dermatofibrosarcoma protuberans, imatinib, resistance, Sunitinib, efficacy

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue malignancy that arises most often on the head, neck and proximal extremities [1-2]. Wide excision is preferred, but with a high rate (about 1%-4%) of recurrences and a tendency of metastasis [3-5] to organs such as the lung and liver, and it becomes more difficult for treatment if there is any metastasis and recurrences. DFSP responds poorly from chemotherapy and radiotherapy. Studies have demonstrated that more than 90% DFSP features the translocation between chromosomes 17q22 and 22q13, which causes the fusion between COL1A1 and PDGFB, the activation of PDGFB activates the signal pathway of PDGFR tyrosine kinase and leads DFSP growth as a result [6-11]. Imatinib is a tyrosine-kinase inhibitor,

with a specific inhibition function of BCR/ABL, KIT, PDGFR- α and PDGFR- β , it can inhibit abnormal signal transduction pathways and tumor growth [12, 13]. In 2002, Maki et al [14] reported a benefit from Imatinib therapy for locally advanced, unresectable and distantly metastatic DFSP for the first time and the results of small sample studies in recent years have shown that Imatinib has become the first choice of targeted therapy. However, Imatinib resistance invariably develops in its widespread use, the further treatment after resistance becomes a big challenge and there are no identified therapeutic options. We treated 95 locally advanced or metastatic DFSP patients with Imatinib from January 2003 and December 2009 and tried Sunitinib for 30 patients after Imatinib failure, most patients experienced objective response as reported below.

Table 1. Patients characteristics in Imatinib treatment group

	Total (n=95)
Age (Median/range), yr	50.0 (18-72)
Gender (male:female)	55:40
Tumor location (n, %)	
Trunk	57 (60)
Limbs	38 (40)
Tumor recurrence (n, %)	
Lung	45 (47.3)
Liver	10 (10.5)
Local recurrence	40 (42.1)

Materials and methods

Materials

Enrollment: We collected data of 95 patients with pathologically defined stage IV DFSP treated with imatinib between January 2003 and December 2009. Other enrollment criteria include stage IV classified by UICC TNM system, locally advanced and distantly metastatic disease, at least one measurable or estimable tumor lesion, KPS \geq 60, expected survival more than 3 months, no vital organ dysfunction, and normal function of heart, liver, kidney and blood routine.

Methods

All patients were assigned to take Imatinib mesylate from Novartis (400 mg) orally once daily in the morning until disease progression or unacceptable toxicity.

Evaluation

We completed baseline factors assessment within one week before the treatment, including clinical evaluation, chest CT and enhanced MRI of vital organs such as the liver, bone and head. And we evaluated the efficacy after 3 months according to the Response Evaluation Criteria in Solid Tumors (RECIST) of the World Health Organization (WHO), by complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and disease control rate (CR+PR+SD). PD was consequently discontinued and all lesions were evaluated every 6 months. The survival was calculated from the beginning of treatment to disease progression, any death or the end of follow-up. The primary endpoint was progression-

free survival (PFS) as the major index for long-term efficacy and the second endpoint was overall survival (OS). PFS was defined as the duration between the beginning of Imatinib or Sunitinib therapy and the time of progression. OS was related to the survival and death after Imatinib or Sunitinib therapy. Adverse effects were observed and recorded from grade 0 to grade IV according to the Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute (NCI).

Statistical analysis

SPSS15.0 software was used for statistical analysis and the Kaplan-Meier method was used to estimate the survival.

Results

Patients characteristics in Imatinib treatment group

95 patients with pathologically defined stage IV DFSP were treated with Imatinib between January 2003 and December 2009, aged from 18 years to 72 years, with a median age of 52, 50 men and 45 women, and the metastasis mostly involved the lung, local soft tissue and the liver (**Table 1**).

Efficacy of Imatinib treatment

During a median follow-up of 4.4 years (3-10.5 years), All 95 patients were evaluable for the efficacy evaluation: 16 had CR (16.8%), 44 had PR (46.3%), 23 had SD (24.2%) and 12 had PD (12.6%). The one-year DCR (CR+PR+SD) was 87.4%. The median PFS was 23 months and the OS was 40 months (**Figures 1 and 2**).

Adverse effects of Imatinib treatment

Adverse events which occurred most often with Imatinib therapy were generally moderate (grade 1-2), including nausea (49%), water retention/edema (30%), fatigue (30%), neutropenia (28%), low platelet count (20%), diarrhea (22%) and skin rash (10%), the majority of adverse effects could be managed well by symptomatic treatment and supportive care.

Efficacy of Sunitinib treatment after Imatinib resistance

From January 2008 to December 2011, we selected 30 Imatinib-resistant patients to

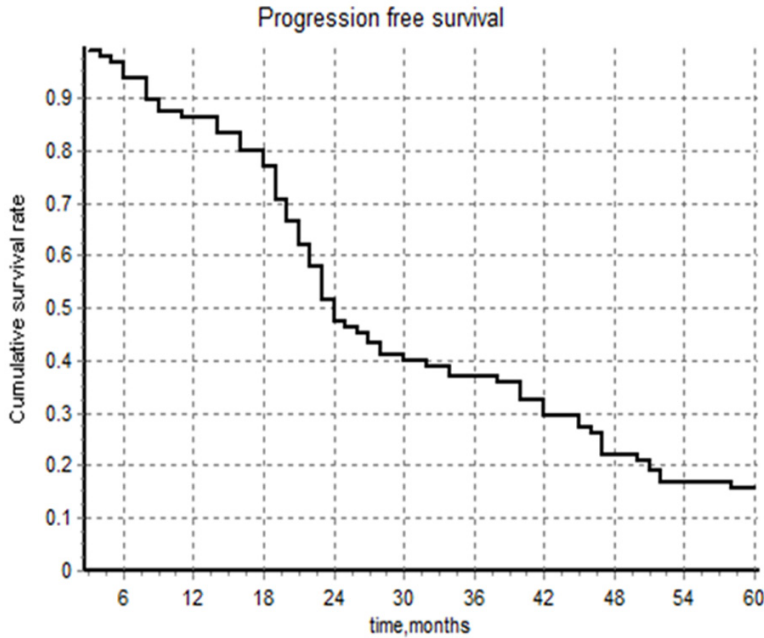


Figure 1. Progression-free survival of DFSP patients treated with Imatinib.

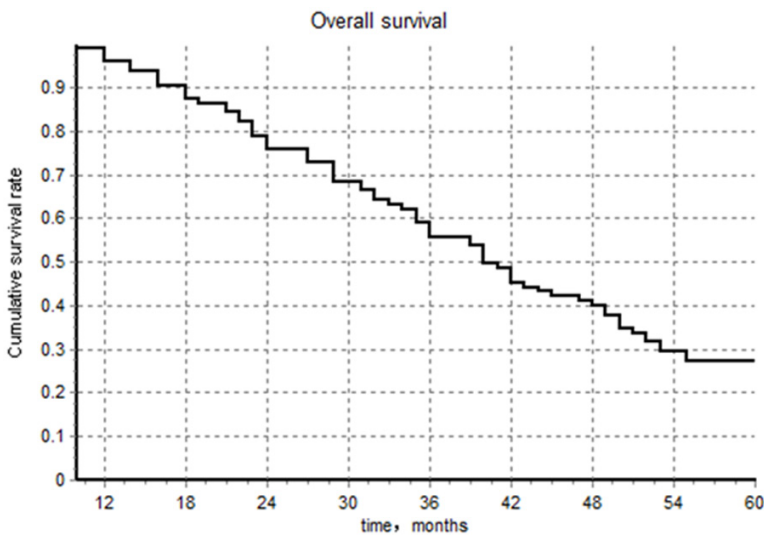


Figure 2. Overall survival of DFSP patients treated with Imatinib.

switch over to Sunitinib therapy, prior to Sunitinib, patients could undertake other chemotherapy (4 weeks before Sunitinib), radiotherapy and local operation. 30 patients either took daily oral Sunitinib (50 mg) by Pfizer for continuous 4 weeks, discontinued 2 weeks for observation and then underwent the second cycle, or took continuous daily oral Sunitinib (37.5 mg), with food or not, until disease progression or unacceptable toxicity. 30 patients were all evaluable for the efficacy evaluation at

the end of follow-up, the median follow-up time was 2.5 years (2-5.6 years), including 2 CR (6.7%), 10 PR (33.3%), 12 SD (40%), and 6 PD (20%). The DCR (CR+PR+SD) was 80%. The PFS of CR and PR was 22 and 20 months respectively, no OS was achieved. The PFS of 12 SD was 18 months and OS was 28 months. The median PFS and OS of all 30 patients were 19 months and 27 months after Sunitinib treatment (Figures 3 and 4, Table 2).

Adverse effects of Sunitinib treatment

The main adverse effects were hand-foot syndrome (63.3%), fatigue (46.7%), Thrombocytopenia (36.7%), Anemia (30%) and hypertension (30%) (Table 3). Adverse events were generally moderate (grade 1-2) and could be managed well by symptomatic treatment and supportive care.

Discussion

Dermatofibrosarcoma protuberans (DFSP) is a very rare type of soft tissue sarcoma which presents in all ages, most often in adults in their thirties, with a slight male predominance and is usually found on the dermis and subcutaneous tissue of the trunk, inguen, rarely of head and neck. Wide surgical resection

is generally accepted as the optimal treatment for DFSP and a complete surgical resection with margins of 3 cm (recommended) of normal tissue, deep fascial and muscle involved is preferred [8-10]. The curative effect of radiotherapy to the disease is affirmed gradually. Hass et al. [25, 26] compared the result of 21 patients treated with surgical resection and 33 patients treated with surgery plus radiotherapy and found that 67% and 82% DCR were achieved respectively. Therefore, radiotherapy plus sur-

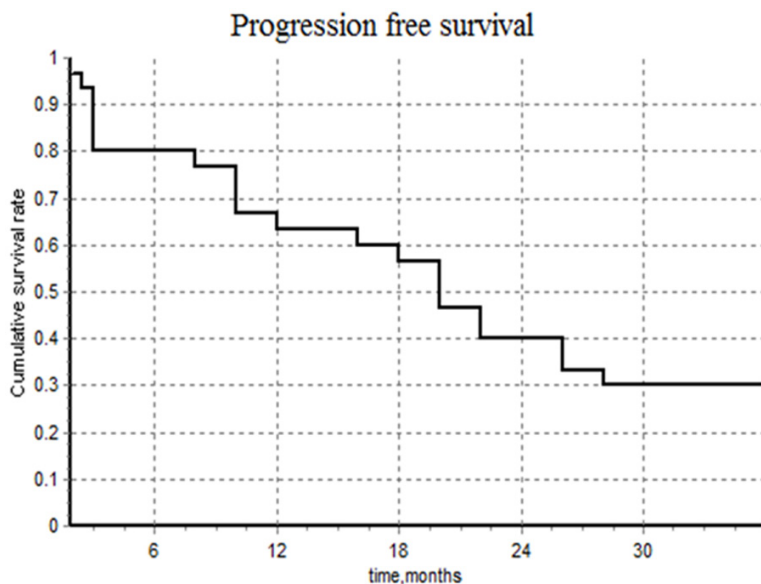


Figure 3. Progression free survival of metastatic DFSP patients treated with Sunitinib after Imatinib resistance.

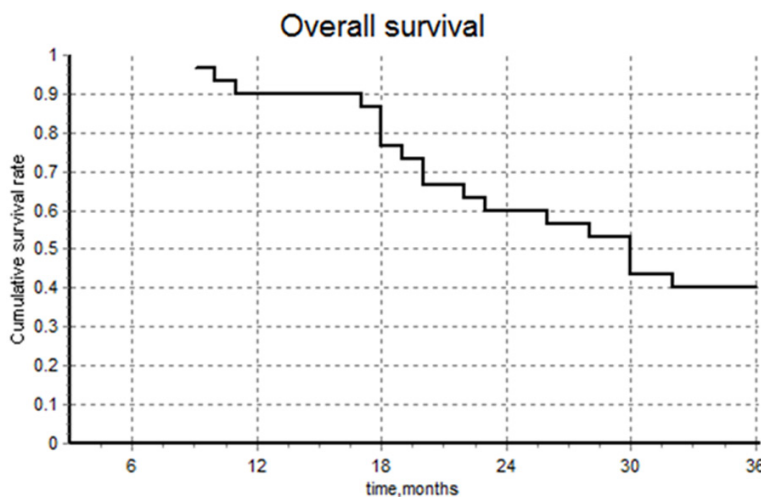


Figure 4. Overall survival of metastatic DFSP patients treated with Sunitinib after Imatinib resistance.

gery was proved to reduce the risk of local recurrence. However, DFSP is characterized by a high recurrence rate, about 24% to 90% DFSPs recur locally and about 1% to 4% distantly metastasize.

Studies in recent year have discovered that the incidence of DFSP is related with a reciprocal chromosomal translocation, t (17; 22) and constitutive activation of the platelet-derived growth factor β -chain (PDGF- β). This rearrangement produces superovulation ring chromo-

some [r (17; 22)] or transposition chromosome [r (17; 22)], and fuses the collagen type I alpha1 (COL1A1) gene with the platelet-derived growth factor β -chain (PDGF- β) gene. And the chromosomal rearrangement causes unregulated expression of PDGF- β , generates functional platelet-derived growth factor, combines and activates platelet derived growth factor receptor in tumor cells, produces autocrine and/or paracrine factor stimulating cell growth and differentiation, causes malignant transformation, and finally result in DFSP tumorigenesis and metastasis. As a potent inhibitor of several protein tyrosine kinases, Imatinib selectively inhibits the expression of PDGFR- β , ABC and KIT kinase. And clinical evidences suggest that Imatinib has revolutionized the treatment of advanced gastrointestinal stromal tumor (GIST) and chronic myelogenous leukemia (CML). Good results were achieved in the treatment of DFSP in 2002, other small sample studies and case reports also demonstrated that Imatinib was an effective treatment for DFSP as a tyrosine kinase inhibitor, especially for those who have abnormal expression of PDGF- β and its receptor. McArthur et al. [27] reported Imatinib

treatment for 10 DFSP patients in 2005 at a dose of 800 mg/d with a result of 4 complete responses in 8 locally advanced DFSP patients. Rutkowski et al. [28] analyzed pooled data of two phase II trials (SWOG-S0345 and EORTC 62027) and revealed 46% response, 58% one-year PFS, and 1.7 year TTP with Imatinib treatment. Jianhua Zhu et al. [29] analyzed 24 advanced DFSP patients treated with Imatinib and found 83.3% DCR and 30 months median overall survival. Therefore, Imatinib was recommended by the Food and Drug Administration

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Table 2. Antitumor response of advanced DFSP patients after Sunitinib treatment

	Patients (n=30)	PFS (median, months)	OS (median, months)
CR (n, %)	2 (6.7)	22	NA
PR (n, %)	10 (33.3)	20	NA
SD (n, %)	12 (40.0)	18	28
PD (n, %)	6 (20.0)	3	11

Table 3. Adverse events of Sunitinib treatment

Adverse event	Sunitinib (n=30)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	4	4	1	0
Hand-foot syndrome	8	9	2	0
Anorexia	5	2	0	0
Diarrhea	4	1	0	0
Constipation	1	0	0	0
Fatigue	9	4	1	0
Vomiting	6	2	0	0
Rash	5	4	0	0
Skin discoloration	5	0	0	0
Mucositis/stomatitis	4	0	0	0
Fever	2	0	0	0
Anemia	5	4	1	0
Leukopenia	5	3	1	0
Thrombocytopenia	6	5	0	0

(FDA) for treating locally advanced, unresectable or distantly metastatic DFSP. 95 patients were enrolled for Imatinib treatment in our study, 16 had CR (16.8%), 44 had PR (46.3%), 23 had SD (24.2%) and 12 had PD (12.6%). The disease control (CR+PR+SD) was 87.4%. The median PFS was 23 months and OS was 40 months. The regimen showed a definite effect and good tolerance since most toxicities were grade 1 and 2, which was consistent with previous reports.

With the widespread use of Imatinib, the occurrence of resistance increases, especially in CML and GIST. At present, the resistance can be solved by dose increasing or regimen change, for example, Dasatinib is used for CML [30-32] and Sunitinib is used for GIST after Imatinib resistance. But there is no clear guidance on therapeutic option once DSFP patients become resistant to Imatinib. Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor, competitively inhibits PDGF-R and vascular

endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), KIT gene (CD117), RET, CSF-1R and flt3. And studies have proven a clear efficacy of Sunitinib on other soft tissue sarcoma [21-24]. We treated 30 DFSP patients after Imatinib resistance from 2008, and found 2 complete responses (6.7%), 10 partial responses (33.3%), 12 stable disease (40%) and 6 progressive disease (20%). The disease control rate was 73.3%, the progression-free survival of complete and partial responses was 22 months and 20 months respectively. The progression-free survival of 12 stable diseases was 18 months, the progression-free survival and overall survival of all patients enrolled was 19 and 27 months.

VEGF and PDGF are the most important regulatory factors that stimulates in both vasculogenesis and angiogenesis [34, 35]. VEGF binds to its receptor VEGFRs, especially trigger signaling network, cause the survival, mitosis, migration and differentiation of epithelial cells, and stimulates vascular permeability and tumor lymphangiogenesis. The collation with tumor angiogenesis and pathogenesis has been clearly defined. Sunitinib is an inhibitor of VEGF receptor, which can inhibit the activity of VEGFR-1, VEGFR-2 and VEGFR-3, block the action of VEGF and its receptors, choke off tumor blood supply by blocking growth signals, thus suppressing cell proliferation and metastasis, which may be one of the reasons for Sunitinib clinical benefit. The mechanism of Imatinib resistance is still unclear, in 2013, Jung Yong Hong et al. [33] used gene sequencing method to compare the gene mutation of 1 DSFP patient before and after Imatinib resistance and they found eight emerged non-synonymous somatic mutations of genes (ACAP2 CARD10, KIAA0556, PAAQR7, PPP1R39, SAFB2, STARD9 and ZFYVE9) in tumor tissues after Imatinib resistance, which provided a direction for future research. However, more efforts are needed for the specific mechanism.

In summary, Imatinib mesylate is an effective treatment for locally advanced, unresectable or distantly metastatic DFSP. Sunitinib shows certain efficacy with tolerable toxicities, and offers a new treatment option for Imatinib-resistant DSFP.

Disclosure of conflict of interest

None.

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References

- [1] Gloster HM Jr. Dermatofibrosarcoma protuberans. *J Am Acad Dermatol* 1996; 35: 355-374.
- [2] Laskin WB. Dermatofibrosarcoma protuberans. *CA Cancer J Clin* 1992; 42: 116-125.
- [3] Chang CK, Jacobs IA, Salti GI. Outcomes of surgery for dermatofibrosarcoma protuberans. *Eur J Surg Oncol* 2004; 30: 341-345.
- [4] Kimmel Z, Ratner D, Kim JY. Peripheral excision margins for dermatofibrosarcoma protuberans: a metaanalysis of spatial data. *Ann Surg Oncol* 2007; 14: 2113-2120.
- [5] Bowne WB, Antonescu CR, Leung DH, Katz SC, Hawkins WG. Dermatofibrosarcoma protuberans: A clinicopathologic analysis of patients treated and followed at a single institution. *Cancer* 2000; 15; 88: 2711-2720.
- [6] Naeem R, Lux ML, Huang SF, Naber SP, Corson JM, Fletcher JA. Ring chromosomes in dermatofibrosarcoma protuberans are composed of interspersed sequences from chromosomes 17 and 22. *Am J Pathol* 1995; 147: 1553-1558.
- [7] O'Brien KP, Seroussi E, Dal Cin P. Various regions within the alpha-helical domain of the COL1A1 gene are fused to the second exon of the PDGFB gene in dermatofibrosarcomas and giant-cell fibroblastomas. *Genes Chromosomes Cancer* 1998; 23: 187-193.
- [8] Nishio J, Iwasaki H, Ishiguro M. Supernumerary ring chromosome in a bednar tumor (pigmented dermatofibrosarcoma protuberans) is composed of interspersed sequences from chromosomes 17 and 22: a fluorescence in situ hybridization and comparative genomic hybridization analysis. *Genes Chromosomes Cancer* 2001; 30: 305-309.
- [9] Sirvent N, Maire G, Pedeutour F. Genetics of dermatofibrosarcoma protuberans family of tumors: from ring chromosomes to tyrosine kinase inhibitor treatment. *Genes Chromosomes Cancer* 2003; 37: 1-19.
- [10] Takahira T, Oda Y, Tamiya S. Detection of COL1A1-PDGFB fusion transcripts and PDGFB/PDGFRB mRNA expression in dermatofibrosarcoma protuberans. *Mod Pathol* 2007; 20: 668-75.
- [11] Patel KU, Szabo SS, Hernandez VS. Dermatofibrosarcoma protuberans COL1A1-PDGFB fusion is identified in virtually all dermatofibrosarcoma protuberans cases when investigated by newly developed multiplex reverse transcription polymerase chain reaction and fluorescence in situ hybridization assays. *Hum Pathol* 2008; 39: 184-193.
- [12] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. *N Engl J Med* 2007; 356: 115-124.
- [13] Demetri GD, van Oosterom AT, Garrett CR. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: A randomized controlled trial. *Lancet* 2006; 14; 368: 1329-1338.
- [14] Maki RG, Awan RA, Dixon RH. Differential sensitivity to Imatinib of 2 patients with metastatic sarcoma arising from Dermatofibrosarcoma Protuberans. *Int J Cancer* 2002; 100: 623-626.
- [15] Osusky KL, Hallahan DE, Fu A, Ye F, Shyr Y, Geng L. The receptor tyrosine kinase inhibitor SU11248 impedes endothelial cell migration, tubule formation, and blood vessel formation in vivo, but has little effect on existing tumor vessels. *Angiogenesis* 2004; 7: 225-233.
- [16] Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Mol Cancer Ther* 2003; 2: 471-478.
- [17] Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; 9: 327-337.
- [18] Murray LJ, Abrams TJ, Long KR. SU11248 inhibits tumor growth and CSF-1R dependent osteolysis in an experimental breast cancer bone metastasis model. *Clin Exp Metastasis* 2003; 20: 757-766.
- [19] O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, Wong LM, Hong W, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC, Cherrington JM. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. *Blood* 2003; 101: 3597-3605.
- [20] Schueneman AJ, Himmelfarb E, Geng L, Tan J, Donnelly E, Mendel D, McMahon G, Hallahan DE. SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. *Cancer Res* 2003; 63: 4009-4016.

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- [21] Penot P, Bouaziz JD, Battistella M. Stabilization of multiple metastatic epithelioid sarcoma under treatment with sunitinib malate. *Br J Dermatol* 2013; 168: 871-873.
- [22] Stacchiotti S, Negri T, Zaffaroni N. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol* 2011; 22: 1682-1690.
- [23] Suzanne George, Priscilla Merriam, Robert G. Maki. Multicenter Phase II Trial of Sunitinib in the Treatment of Nongastrointestinal Stromal Tumor Sarcomas. *JCO* 2009; 27: 3154-3160.
- [24] Stacchiotti S, Negri T, Libertini M. Sunitinib malate in solitary fibrous tumor (SFT). *Ann Oncol* 2012; 23: 3171-3179.
- [25] Sun LM, Wang CJ, Huang CC. Dermatofibrosarcoma protuberans: treatment results of 35 cases. *Radiother Oncol* 2000; 57: 175-181.
- [26] Dagan R, Morris CG, Zlotecki RA. Radiotherapy in the treatment of dermatofibrosarcoma protuberans. *Am J Clin Oncol* 2005; 28: 537-539.
- [27] McArthur GA, Demetri GD, van Oosterom A. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. *J Clin Oncol* 2005; 23: 866-873.
- [28] Rutkowski P, Glabbeke MV, Rankin CJ. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. *J Clin Oncol* 2010; 28: 1772-1779.
- [29] Jiahua Zhu, Qiuwen Li, Wenhua Xiao. Advanced Dermatofibrosarcoma Protuberans treated with imatinib mesylate. *Chin J Oncol* 2011; 33: 470-473.
- [30] Breccia M, Alimena G. The current role of high-dose imatinib in chronic myeloid leukemia patients, newly diagnosed or resistant to standard dose. *Expert Opin Pharmacother* 2011; 12: 2075-2087.
- [31] Quintás-Cardama A, Cortes J. Therapeutic options against BCR-ABL1T315I-positive chronic myelogenous leukemia. *Clin Cancer Res* 2008; 14: 4392-4399.
- [32] Weisbeg E, Manley PW, Cowan-Jacob SW. Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. *Nat Rev Cancer* 2007; 7: 345-356.
- [33] Hong JY, Liu X, Mao M, Li M, Choi DI, Kang SW, Lee J, La Choi Y. Genetic Aberrations in Imatinib-Resistant Dermatofibrosarcoma Protuberans Revealed by Whole Genome Sequencing. *PLoS One* 2013; 8: e69752.
- [34] Pan X, Mao T, Fang W, Chen W. Vascular endothelial growth factor C is an indicator of lymph node metastasis in thoracic esophageal squamous cell carcinomas and its role in long-term survival after surgery. *Thoracic Cancer* 2014; 5: 313-318.
- [35] Zhuo Y, Guo Q, Song P, Zhang Q, Guo C, Zeng H, Guan Y, Liu X, Zhao C. Correlation study and significance of the EGFR expression in serum, lymph nodes and tumor tissue of NSCLC. *Thoracic Cancer* 2014; 5: 31-37.