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CASE REPORT

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A new therapeutic approach in patients with advanced sarcoma

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Abstract Sarcomas represent a rare and heterogeneous disease and the prognosis of patients remains poor, with a disease-free survival at 5 years of less than 10%. Only a few chemotherapeutic agents, such as doxorubicin and ifosfamide, have been identified to be active with response rates above 20%. The concept of angiostatic therapy in combination with proapoptotic biomodulators and chemotherapeutics has not been evaluated in these patients. Therefore, the efficacy of low-dose trofosfamide in combination with the peroxisome proliferator-activated receptor-γ-agonist, pioglitazone, and the selective cyclooxygenase-2 inhibitor, rofecoxib, was evaluated in a pilot study. Six patients with advanced sarcoma received a combination of oral pioglitazone plus rofecoxib and, after 14 days, oral trofosfamide. The therapy was administered continuously daily. Four patients received the triple combination as maintenance therapy; three of them achieved stabilization of disease. Two patients received the combination as relapse therapy; however, it failed to stop disease progression. Side effects were generally mild and hospitalization was not necessary. This new triple combination of low-dose trofosfamide, pioglitazone, and rofecoxib may represent a feasible new alternative in the palliative treatment of sarcoma patients.

Key words Antiangiogenic · Oral · Proapoptotic · Sarcoma

Introduction

The prognosis of patients with advanced bone and soft-tissue sarcoma (STS) remains poor, with a disease-free survival of less than 10% at 5 years. Only a few chemotherapeutic agents, such as doxorubicin and ifosfamide, have been identified to be active with response rates above 20%. Alternative strategies are lacking. The concept of antiangiogenic therapy in combination with proapoptotic biomodulators and chemotherapeutics has not been evaluated. Therefore, the efficacy of low-dose trofosfamide in combination with the peroxisome proliferator-activated receptor-γ-agonist, pioglitazone, and the selective cyclooxygenase-2 (COX-2) inhibitor, rofecoxib, was evaluated in a pilot study.

Antiangiogenic therapy uses the endothelial cells of the host as a reliable therapeutic partner, a strategy independent of the heterogeneity of the tumor itself. A correlation of circulating angiogenic factor levels with extent of disease and risk of recurrence was demonstrated in patients with STS.[1] Low-dose chemotherapy, targeting the proliferating endothelial cells that supply the tumor, has shown convincing data in terms of tumor reduction and disease stabilization. The combined application of additional drugs with apoptosis-inducing potential may be superior in these complex patients. Pioglitazone induces apoptosis in tumor cells in vivo and in vitro, and suppresses tumor growth by direct and indirect antiangiogenic effects.[2] Rofecoxib suppresses tumor-associated angiogenesis partly by interference with prostaglandin metabolism.[3] The first results using this treatment strategy were reported in patients with melanomas and angiosarcomas, by Vogt et al.[4] and Reichle et al.[5]

Case report

Six patients (median age, 48.0 years) with histologically proven bone and STS were eligible for this pilot study (3 patients had leiomyosarcomas; 1, synovial sarcoma; 1, neurofibrosarcoma; and 1, chondrosarcoma). The research was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions; informed consent was obtained; and the relevant institutional review board had approved the study. Five patients had been pretreated with high-dose chemotherapy followed by autologous peripheral-blood stem-cell transplantation.

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Table 1. Patients' characteristics and response to therapy

Patient no.	Sex	Age (years)	Diagnosis	Metastatic sites	Pretreatment	Response (after 3 months)	PFS (months)	OS (months)
1	F	55	Synovial sarcoma	Pulmonary	Surgery, HDCT + ABSCT	PD	3	8[b]
2	F	60	Leiomyo-sarcoma	Pulmonary	HDCT + ABSCT	PR	12	14[a]
3	M	44	Neuro-fibro-sarcoma	Pulmonary	Surgery, radiotherapy, HDCT + ABSCT	PD	2	6[b]
4	M	40	Leiomyo-sarcoma	Pulmonary, liver	Surgery, HDCT + ABSCT	PD	0	3[b]
5	F	25	Chondro-sarcoma	Pulmonary	HDCT + ABSCT	NED	9	9[a]
6	M	64	Leiomyo-sarcoma	Abdominal, bone	Surgery, chemotherapy	PR	10	10[a]

PFS, progression-free survival; OS, overall survival; HDCT, high-dose chemotherapy; ABSCT, autologous-blood stem-cell transplantation; NED, no evidence of disease; PR, partial remission; PD, progressive disease
[a] Patient is still alive
[b] Patient died in this month

Further pretreatments included surgery, radiotherapy, or conventional chemotherapy. The patients' characteristics as well as their responses to therapy are summarized in Table 1.

Triple therapy consisted of oral pioglitazone 45 mg and rofecoxib 25 mg per day, starting on day 0, with the addition of oral trofosfamide 3×50 mg per day starting on day 15.

Four patients received therapy as maintenance treatment after high-dose chemotherapy with autologous stem-cell rescue (cases 2, 3, 5, and 6): two patients (cases 2 and 6) achieved partial remission and stayed progression-free for 12 and 10 months, respectively; one patient (case 5) with no evidence of disease (NED) stayed disease-free for 9 months; the fourth patient (case 3) died 6 months after the start of treatment due to progressive disease (PD). Two patients received the regimen as relapse therapy (cases 1 and 4): treatment failed to stop disease progression; the patients died after 8 and 3 months, respectively. Median progression-free survival (PFS) for all patients was 6.0 months (range, 0–12 months), and median overall survival (OS) was 8.3 months (range, 3–14 months); survival was twice as long as that in a previous study.[5] Survival was better for the patients who received treatment as maintenance therapy, with their PFS being 8.3 months (range, 2–12 months) and OS 9.8 months (range, 6–14 months).

Side effects were mild and hospitalization was not necessary. Rofecoxib was not given in one patient (case 3) because of known asthma, and it was stopped in another patient (case 6) after 1 month because of grade 1 nephrotoxicity.

Discusssion

This report of a new therapeutic approach with pioglitazone, rofecoxib, and trofosfamide demonstrated efficacy in the care of patients with progressive and metastatic sarcoma. Only six patients were included to obtain preliminary data for further investigations. However, statistical analysis could not be performed due to the small sample size.

We tested an alternative approach to palliative treatment for sarcoma patients, based on recent research results regarding antiangiogenic and proapoptotic tumor therapy. The first results of this antiangiogenic treatment regimen in human angiosarcomas were reported by Vogt et al.[4] Three of their six patients (50%) responded with a complete remission (from 6 months to ≥15 months) or an overall response (≥7 months).

Two different antiangiogenic mechanisms were combined in our pilot study: first, the biomodulating drugs pioglitazone and rofecoxib were applied. Both drugs are approved for the treatment of metabolic and rheumatic diseases, and are efficient in the inhibition of angiogenesis. Second, the classical oral cytotoxic drug trofosfamide was administered continuously at a low dose to target both the tumor cells and the slowly proliferating tumor endothelial cells. Due to the low dose, the toxicity was tolerable, and the therapy was tolerated very well by the patients.[6]

As rofecoxib was withdrawn in October 2004, treatment with rofecoxib has been stopped in all patients. In a study treating patients with colon adenomas with rofecoxib 25 mg daily, a higher cardiovascular risk had been shown in comparison to those who had been treated with placebo. Nevertheless, these adverse events were only demonstrated after a treatment time of more than 18 months. None of our patients received rofecoxib for such a long time. In further studies we will use etoricoxib as an alternative COX-2 inhibitor.

The promising results of our case report indicate that the combination of trofosfamide, pioglitazone, and rofecoxib may be a feasible alternative in the treatment of sarcoma patients, especially in the setting of maintenance therapy; as relapse therapy, it failed to stop disease progression. There are great benefits in terms of efficacy, low toxicity, and quality of life with this novel approach. Of course, no general conclusions can be drawn from our small sample size, and we are currently investigating this approach in ongoing phase II studies.

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