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SHORT COMMUNICATION

Trabectedin in advanced soft tissue sarcoma: case series

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Summary

The prognosis of advanced soft tissue sarcomas (STS) is poor. The median overall survival (OS) is 6 months in unresectable and metastatic STS that progress after treatment with anthracyclines and ifosfamide. Trabectedin is an alkylating agent, effective in advanced STS, especially in leiomyosarcoma and liposarcoma. In the present study, the effectiveness and safety of trabectedin was retrospectively evaluated in 8 unresectable and metastatic STS patients. Their median age was 47 years. The median progression free survival (PFS) was 3.75 months and the median OS 15 months in relapse or progression after anthracyclines and/or ifosfamide. Toxicities were mainly hematologic. In the present study, trabectedin showed efficacy in different histological subtypes of sarcomas like liposarcoma and leiomyosarcoma.

Key words: anthracycline, ifosfamide, soft tissue sarcoma, trabectedin

Introduction

STS are a heterogeneous group of mesodermal tumors. They comprise 1% of all adult malignancies. Survival is not promising except for patients undergoing radical surgical tumor removal in early disease stages. While 5-year survival rate in all groups is 50-60%, it decreases to 10% in unresectable and metastatic patients [1]. Prognosis is poor with median OS of only 6 months in STS cases that progress after treatment with anthracyclines and ifosfamide [2]. Obviously, there is a need for effective alternative treatment options in this patient group.

Trabectedin (Ecteinascidin-743, Yondelis^{TM}) is an alkylating agent derived from the caribbean marine tunicate, which blocks the cell cycle in late S and G2 phases [1]. Its effectiveness on STS is demonstrated in phase I and II studies [3-5]. Median OS ranges between 8 and 13 months after first-line treatment with anthracyclines and ifosfamide, and 6 months after standard chemotherapy failure [2]. In a phase I study including 20 advanced-stage STS patients, complete response (CR) was observed in one patient and partial response (PR) in 3 [4]. Trabectedin's response rate is around 10%, with a 10% 1-year PFS, while it seems to be especially effective in leiomyosarcoma and liposarcoma [5-7]. While the response rate of trabectedin in 92 patients from compassionate use programs and phase II clinical trials between 1999 and 2006 was 10%, disease stabilisation was attained in 28% of the patients. Median PFS and median OS in all patients were 2.2 months and 8.9 months, respectively [8]. In a phase II study including 270 STS patients, which compared 3-weekly and weekly administration of trabectedin, the 6-month PFS (35.5 vs. 27.5%) and the median OS (13.9 vs. 11.8 months) were higher in the 3-weekly arm of the study [5].

Results

In the present short communication, the effectiveness and safety of trabectedin was retrospectively evaluated in 8 unresectable and metastatic STS patients with failure after conventional chemotherapy with anthracyclines and ifosfamide. Trabectedin was administered as a 1.5 mg/m^2 24-h infusion, once every 3 weeks. The median patient age (7 females, 1 male) was 47 years (range

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Table 1. Disease, survival and toxicity characteristics

Primary tumor localization	*Pathology*	*No. of lines**	*No. of cycles§*	*Median PFS (mos)*	*Median OS (mos)*	*Toxicity*
Uterus	Mesenchymal Sa	3	2	3.5	15	G1 thrombocytopenia, G3 neutropenia, G3 skin toxicity
Uterus	Leiomyo Sa	3	6	11	25	None
Retroperitoneum	Pleomorphic undif. Sa	2	4	5	13	G1 hepatotoxicity, G2 asthenia
Retroperitoneum	Leiomyo Sa	4	3	3	4	G2 anemia, G2 neutropenia
Right thigh	Synovial Sa	3	12	12	16	G2 anemia, G3 neutropenia
Right thigh	Lipo Sa	4	3	3.5	8	G3 skin toxicity, G3 neutropenia
Left hip	Lipo Sa	3	1	2	LFU	None
Right ankle	Leiomyo Sa	3	4	6	20	G2 asthenia, G1 neutropenia

G: grade, Sa: sarcoma, Undif: undifferentiated, No: number, LFU: lost to follow up, mos: months, PFS: progression free survival, OS: overall survival, *number of previous chemotherapy lines, §number of trabectedin cycles

22-51). All patients presented with local signs of the tumor. There were 3 patients with leiomyosarcoma, 2 with liposarcoma, and the remaining 3 patients had synovial cell sarcoma, pleomorphic sarcoma, and mesenchymal sarcoma. Localization was intra-abdominal in 4 patients and in the extremities in 4. While 6 patients had surgery, the disease was unresectable in 2. Three patients had metastatic disease at diagnosis; 2 had lung, and 1 lung and bone metastasis. Trabectedin was administered as 3rd line in 5 patients, 4th line in 2, and 2nd line in 1 patient (Table 1). In unresectable or metastatic cases that relapsed or progressed after combined or consecutive regimens of anthracyclines and ifosfamide, the median PFS was 3.75 months (range 2-12) and the median OS 15 months (range 4-25; Table 1). Dose was reduced from 1.5 to 1.25 mg/m^2 in 2 patients. Grade 1 and 2 toxicities were hematologic (n=5), asthenia (n=2), and hepatotoxicity (n=1); grade 3 hematologic toxicity and grade 3 skin toxicity were observed in 3 and 2 patients, respectively.

In a recent study, trabectedin was terminated early in 4.6% of the patients due to side effects [5]. The most common side effects are weakness, fatigue, nausea, vomiting, constipation, diarrhea, and headache, while neutropenia, liver enzyme increase, and rhabdomyolysis have been reported as serious side effects. Hepatotoxicity and hematologic toxicity have been reported as the most common serious side effects in compassionate use programs and clinical trials. In our study, in line with the literature, hematologic toxicity and asthenia were observed most frequently, yet no treatment was terminated due to toxicity. Grade 3 skin toxicity, observed in 2 patients, was higher than the literature entails.

Toxicity and survival rates in our study were quite similar to those found in the literature. Also trabectedin showed efficacy in different histologic subtypes of STS. Trabectedin is a treatment option for unresectable and metastatic STS patients who relapse or progress after standard treatments.

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