Wspolczesna Onkol 2011; 15 (6): 367–371

DOI: 10.5114/wo.2011.26437

Background: Trabectedin is a new cytotoxic drug registered in 2007 for therapy of advanced soft tissue sarcomas in case of failure of treatment with anthracyclines and ifosfamide or in patients who are not eligible for this kind of treatment. Pre-registration studies showed its efficiency in therapy of advanced soft tissue sarcomas.

The aim of the study was to analyse the results of trabectedin therapy in patients with advanced soft tissue sarcoma of selected histological subtypes treated in one oncological centre.

Material and methods: We retrospectively analysed 26 patients treated with trabectedin for advanced soft tissue sarcomas, in the period from 04.2008 to 03.2011. Thirteen patients were diagnosed with leiomyosarcoma, 10 patients with liposarcoma, 2 patients with synovial sarcoma, 1 with pleomorphic sarcoma. All patients were previously treated with chemotherapy.

Results: 120 courses of trabectedin were given (median 4, range 1-20). We were able to assess the response in 24 patients. According to the RECIST criteria responses were as follows: 1 partial response (4%), 12 cases of stable disease (50%), and 11 of progressive disease (46%). The 6-month progression-free survival (PFS) rate was 21%, median PFS was 2.5 months, but in the group of patients who had clinical benefit (PR+SD) the median PFS was 5 months. Tolerance of this treatment was good. In 17 patients adverse events were observed; 5 of them had dose reduction. Mainly there were mild haematological toxicity and hepatotoxicity. 7 patients suffered from grade 3 or 4 toxicity according to CTC v. 4.

Conclusion: We showed that trabectedin is effective and well tolerated by patients treated earlier with many lines of chemotherapy for soft tissue sarcoma.

Key words: trabectedin, sarcoma, chemotherapy, progression free survival, toxicity.

Trabectedin in patients with pre-treated advanced soft tissue sarcoma: a retrospective single center analysis

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Background

Adult soft tissue sarcomas are a highly heterogeneous group of tumours of mesenchymal origin with a low incidence. They account for less than 1% of all adult malignancies [1]. Despite adequate treatment and control of localized disease, approximately 40% to 50% of high-risk STS patients still develop distant metastases and die as a result of disseminated disease [2, 3].

In advanced disease the probability of response to the most active drugs, anthracyclines and ifosfamide, ranges from 20% to 40% [2]. After failure of conventional chemotherapy, there is no standard of care for second-line therapy and median survival is < 1 year [3-5]. Apparently, new agents with effects on soft tissue sarcoma need to be identified to improve treatment in these patients [6].

Trabectedin is a novel tetrahydroisoquinoline compound isolated from the marine ascidian *Ecteinascidia turbinata* [7, 8]. Trabectedin interacts with DNA in a sequence-specific manner, covalently binding a guanine residue in the DNA minor groove and bending it toward the major groove, thus possibly altering DNA interactions with transcription factors and other critical nuclear proteins [9]. Although the objective response rate in patients with anthracycline-resistant advanced STS has not exceeded 10% in multiple phase I and II clinical trials, this drug has resulted in control of disease with progression arrest rates exceeding 50% and progression-free survival (PFS) exceeding 20% at 6 months [10]. The main benefits have been documented in leiomyosarcoma and liposarcoma (which are the most common adult sarcoma subtypes); particular sensitivity to the drug was noted in myxoid liposarcoma subtype [11, 12].

The aim of this study was to assess the therapeutic activity of trabectedin in 26 patients treated in a single reference oncological centre.

Material and methods

Twenty-six patients (13 female and 13 male) were included in this retrospective analysis. Patients were treated at the Department of Soft Tissue/Bone Sarcoma and Melanoma at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland between April 2008 and March 2011. The detailed patient characteristics are shown in Table 1. The median age at the start of trabectedin therapy was 51 years (range 28-71). The most common tumour type was leiomyosarcoma (13 patients; 50%). Ten patients (38%) had liposarcoma; 6 of them (60%) had the type myxoid liposarcoma, two patients (7.6%) had synovial sarcoma and one (3.8%) had pleomorphic sarcoma. Primary sites comprised extremities (35%), abdomen/retroperitoneum (31%), trunk (15%), uterus (11%), heart (4%), prostate (4%). All patients had

Table 1. Patient characteristics

Patient	Age (at diagnosis)	Gender	Histology	Primary Tumour	Previous CTX lines	Time (months) from diagnosis to start of trabectedin therapy	#Cycles	Result	PFS (months)	Toxicity	Dose reduction
1	34	M	Leiomyosarcoma	Heart	3	13	2	PD	1.5	No	No
2	29	M	Liposarcoma	Extremity	5	39	4	SD	4	Yes	Yes
3	63	F	Leiomyosarcoma	Extremity	2	128	6	SD	7	No	No
4	31	M	Liposarcoma	Trunk	4	37	2	PD	1.5	Yes	No
5	49	M	Leiomyosarcoma	Trunk	2	8	2	PD	1	Yes	No
6	51	F	Liposarcoma	Extremity	2	124	20	SD	25	Yes	Yes
7	20	F	Synovial sarcoma	Extremity	8	88	2	PD	1	Yes	No
8	49	M	Liposarcoma	Retroperitoneum	1	6	5	SD	3	Yes	No
9	39	F	Leiomyosarcoma	Uterus	5	34	4	SD	2.5	Yes	Yes
10	36	M	Leiomyosarcoma	Extremity	3	29	2	PD	1	Yes	No
11	70	M	Leiomyosarcoma	Retroperitoneum	2	N/A	5	SD	5	Yes	No
12	42	M	Synovial sarcoma	Extremity	6	35	6	SD	4	Yes	Yes
13	44	F	Liposarcoma	Extremity	2	119	2	PD	1	Yes	No
14	43	F	Liposarcoma	Retroperitoneum	3	116	8	SD	13	Yes	No
15	41	M	Leiomyosarcoma	Prostate	4	N/A	2	PD	1.5	No	No
16	58	M	Leiomyosarcoma	Retroperitoneum	4	40	4	PR	4	Yes	No
17	51	F	Leiomyosarcoma	Uterus	5	55	5	SD	5	No	No
18	67	F	Leiomyosarcoma	Trunk	3	18	2	PD	1	Yes	No
19	50	M	Leiomyosarcoma	Extremity	4	35	2	PD	1.5	No	No
20	64	F	Leiomyosarcoma	Retroperitoneum	2	10	3	SD	1	Yes	No
21	59	F	Liposarcoma	Retroperitoneum	2	35	2	PD	1	No	No
22	50	M	Leiomyosarcoma	Retroperitoneum	2	20	8	SD	9	Yes	No
23	58	F	Pleomorphic sarcoma	Trunk	5	115	2	PD	1	No	No
24	63	F	Liposarcoma	Retroperitoneum	1	55	8	SD	9	Yes	Yes

M – male, F – female, PR – partial remission, SD – stable disease, PD – progression of disease, N/A – not applicable

been treated with prior chemotherapy. All patients had been previously treated with anthracyclines, and 46% of them had also received prior ifosfamide therapy. The median number of previous chemotherapy regimens was 3 (range 1-8). All patients had locally advanced or metastatic disease at the time of trabectedin treatment initiation. Twenty-four patients were assessable for response.

Eligibility criteria for initiation of treatment with trabectedin were as follows: unresectable/metastatic soft tissue sarcomas with measurable lesion on computed tomography (CT imaging) after documented progression on prior systemic therapy; Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2, and adequate haematological parameters (absolute neutrophil count $\geq 1.5 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l), hepatic parameters [bilirubin ≤ upper limit normal value (ULN); AST/ALT ≤ 2.5 × ULN; total alkaline phosphatase ≤ ULN] and adequate renal function.

A total of 120 cycles were administered, with duration of therapy for individual patients ranging from one to 20 cycles (median number is 4 received cycles). At the time of analysis, one patient was still on treatment. Trabectedin was administered at a dose of 1 mg/m^2 intravenously as 24-h continuous infusion every 3 weeks using a central venous line. The majority of patients (75%) did not require dose reductions. Anti-emesis prophylaxis included ondansetron and corticosteroids (beside their antimimetic activity, it is proved that corticosteroids decrease hepatotoxicity, which is likely to occur during trabectedin treatment [8, 13, 14]).

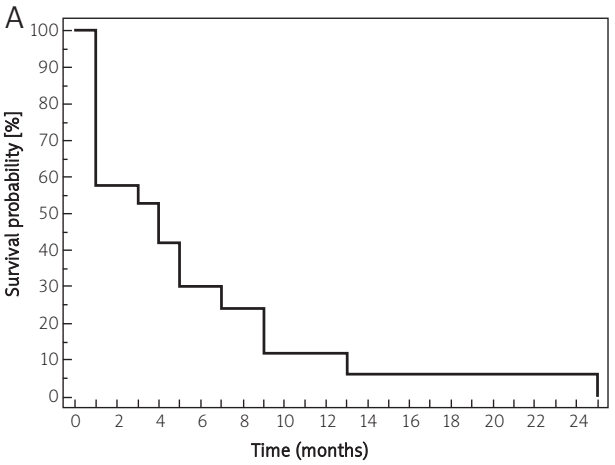

Fig. 1A. Progression-free survival for all patients

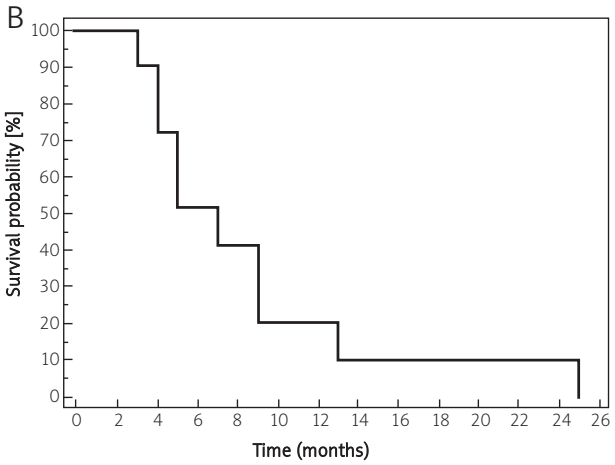

Fig. 1B. Progression-free survival in the group of patients with clinical benefit from therapy with trabectedin

Tumour assessment (by CT) was carried out every two to three cycles. The Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess response.

Statistical calculations were performed using MedCalc software (release 11; Mariakerke, Belgium). The Kaplan-Meier method was used for the analysis of survival curves. Progression-free survival (PFS) time was calculated from the date of the start of trabectedin treatment to radiologically proven disease progression. Overall survival time (OS) was calculated from the date of start of trabectedin treatment to the date of the patient's death or last follow-up (Table 1).

Results

Response assessment and survival

According to the RECIST criteria the best responses observed during trabectedin treatment were: partial response (PR) – 1 patient (4%), stabilization of the disease (SD) – 12 patients (50%), and progression of the disease (PD) – 11 patients (46%). Overall clinical benefit of trabectedin treatment (PR + SD) was 53%. PFS rate at six months for the entire group was 21%, median PFS was 2.5 months. However, in the group of patients who had a benefit of the therapy (PR + SD) the median PFS was 5 months (Fig. 1A, B). Median overall survival (OS) in the whole group of patients was 7 months (range 1-36 months).

Treatment toxicity

Adverse events were common during trabectedin treatment and occurred in 17 of 24 patients, but the majority of them were mild [grade 1-2 according to Common Toxicity Criteria (CTC) v 4] (Table 2). Seven patients suffered from toxicity grade 3-4. Five patients (20.8%) required dose reduc-

Table 2. Haematological and non haematological toxicity per patient during the whole treatment

Toxicity type		Toxicity grade (Common Toxicity Criteria)			
		Grade I	Grade II	Grade III	Grade IV
Haematological toxicity	No. (%)				
WBC		2 (8.3)	3 (12.5)		1 (4.1)
ANC		3 (12.5)	2 (8.3)	1 (4.1)	
Anaemia		2 (8.3)	4 (16.6)	1 (4.1)	
Platelets		3 (12.5)			1 (4.1)
Liver function	No. (%)				
GGTP		2 (8.3)	3 (12.5)	4 (16.6)	1 (4.1)
AlkP		5 (20.8)	1 (4.1)		
Bilirubin		1 (4.1)			
AST/ALT		6 (25)	2 (8.3)		
Kidney function	No. (%)				
Creatinine elevation		1 (4.1)			1 (4.1)

WBC – white blood cells, ANC – absolute neutrophil count, GGTP – glutamyl transpeptidase, AlkP – alkaline phosphatase, AST/ALP – aspartate aminotransferase/alanine aminotransferase

tion due to toxicity not manageable by standard supportive treatment.

One patient after the second cycle of treatment was hospitalized because of febrile neutropenia associated with grade 4 thrombocytopenia and 2 grade anaemia, and with gamma-glutamyl transpeptidase (GGTP) level elevation to grade 3 toxicity. Extended hospitalization was required with transfusion of blood derivative, broad-spectrum antibiotic therapy and administration of granulocyte colony stimulating factors. The next cycles of treatment for this patient were administered in reduced doses, and no such toxicity recurred. In total he was given 6 cycles of treatment, with stabilization of the disease and 4-month PFS.

Among our patients the most common haematological toxicity was grade 1 and 2: 20.8% of them suffered from decrease of white blood cell count, anaemia (25), thrombocytopenia grade 1 was found in 3 patients (12.5%) and grade 4 in one previously mentioned patient (4.1%).

The most common biochemistry abnormalities concerned liver function tests. Elevation of GGTP level was found in 10 patients (41.6%), alkaline phosphatase excess (ALP) concerned 6 patients (25%). Elevated serum bilirubin level was found in one patient (grade 1 – 4.1%). Transaminase levels were increased in 8 patients (33%). Renal dysfunction occurred in 2 of the patients (8.3%). One of them had an increased creatinine serum level to grade 1. The other person after a following cycle of treatment was hospitalized because of grade 4 creatinine level elevation. It is not clear whether the impairment of renal function was strictly associated with the therapy, or it occurred because of the rapid progression of the metastatic tumour in the retroperitoneal space that impaired the urine flow. One female patient suffered from persistent fever of unknown origin associated with significant fatigue. After 8 cycles treatment was completed, at the patient's demand, though obtaining stabilization of the disease. It was the only case of terminating the therapy for reasons other than disease progression (Table 2).

Discussion

Trabectedin was approved in July 2007 by the Committee for Medicinal Products for Human Use in Europe. The European Comminsion has authorized its use, and it is commercially available in several countries in Europe and Japan, where it is marketed for the treatment of STS in adults after failure of standard therapy [15, 16].

The efficacy of trabectedin in the schedule of 24-hour infusion every 3 weeks (q3 weeks 24 hours) in patients with heavily pretreated advanced/metastatic soft tissue sarcoma was evaluated in three main non-randomized phase II clinical studies. The first of them was published in March 2004 by Yovine *et al*. [10] and concerned a group of 54 patients previously treated for advanced/metastatic soft STS, predominantly leiomyosarcoma subtype (41%). Patients received a median of three cycles (range 1 to 20); 28% received six or more cycles. Fifty-two patients were assessable for response; there were two partial responses, four minor responses, and nine with stable disease (? 6 months). Median progression-free survival was 1.9 months (range 0.69 to 17.9 months); 24% of patients were free of progression at month 6. Median overall survival was 12.8 months, with 30% of patients alive at 2 years. Four patients withdrew because of treatment-related toxicity. Two treatment-related deaths occurred that were probably related to protocol eligibility violations [10]. The next study was published in April 2004 by Garcia-Carbonero *et al*. [17], on a group of 36 pretreated patients (the majority of them with leiomyosarcoma or liposarcoma subtype). Objective responses were observed in three patients, with one complete response and two partial responses, for an overall response rate of 8%. Responses were durable for up to 20 months. Two minor responses were observed, for an overall clinical benefit of 14%. The estimated 1-year time to progression and overall survival rates were 9% and 53%, respectively [17]. A larger study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma group included 104 patients with advanced soft tissue sarcomas from eight European institutions. A total of 410 cycles were administered in 99 assessable patients. There were eight PRs (8%), 45 showed no change (NC; > 6 months in 26% of patients), and 39 cases of progressive disease. The median duration of the time to progression was 105 days, and the 6-month progression-free survival was 29%. The median survival was 9.2 months [18].

A few single institution studies on small groups of patients have been published, with similar response rates and toxicity profile [19,20]. Generally, trabectedin has shown slightly better efficacy in leiomyosarcoma and liposarcoma subtypes compared to other STS subtypes [12, 21]. Trabectedin has shown notable efficacy in myxoid liposarcomas [11, 12].

The only randomized phase II trial with trabectedin in pretreated advanced liposarcomas and leiomyosarcomas has confirmed efficacy of 24-hour infusion every 3 weeks regimen for superior disease control as compared to historical control with median overall survival approaching 14 months (in the context of expected 6-month survival range) [21].

The most common toxicities observed in trabectedin studies were grade 3 or 4 transaminase increase (26-59%) and neutropenia (33-52%) [8, 10, 15, 17, 18, 21-23]. These toxicities were manageable and not cumulative with a quite low incidence of relevant clinical consequences [15]. In our study the intensity of toxicity is smaller; this may be a result of lower doses of the drug administered in our institution (1 mg/m^2 rather than 1.5 mg/m^2).

In our study we analysed a group of 24 patients with advanced/metastatic soft tissue sarcoma after failure of standard therapy who have been treated in our institution with trabectedin since 2008. All of them have previously received chemotherapy including doxorubicin, and the majority of those containing ifosfamide. The majority of patients had the leiomyosarcoma or liposarcoma subtype. The mean number of received cycles was 4. An objective response was achieved only in one case (4.1%), but a clinical benefit manifested as stabilization of the tumour was observed in 12 patients (50%). The 6-month progression-free survival rate was 21%, and median overall survival was 7 months. Median time of therapy was 2 months (range 1 to 25 months). 6 patients (25%) received 6 or more cycles of treatment. In the case of one female patient after administration of 20 cycles with sta-

bilization of the disease confirmed by CT, we decided to discontinue treatment, and after one month of observation progression of the disease was observed. That may mean that a group of patients can benefit from long lasting maintenance therapy, which can be challenging taking into account the pharmacoeconomics of the drug. The clinician is thus left with the open issue of how long therapy should be continued in responding/stable patients[12], especially as the toxicity of the drug, in contrast to many traditional chemotherapeutics, is not cumulative [15, 21].

The safety profile is in fact favourable, acute reversible elevation of transaminases being the most prevalent adverse effect [24]. In our studied group of patients more than 70% suffered from adverse events of therapy, the vast majority of them mild (grade 1 and 2 according to CTC v.4). Seven patients (29%) experienced grade 3 or 4 adverse events. One of the patients required hospitalization due to life-threatening toxicity: grade 4 decrease of haematological parameters accompanied by a significant increase of parameters of liver failure. Only one patient discontinued therapy because of poor tolerance of treatment. Particularly noteworthy is the rarity of many of the unpleasant and/or life-threatening effects typical of commonly used anticancer chemotherapeutic agents, such as alopecia, mucositis, skin/nail toxicities, neurotoxicity, cardiac toxicity, or other major organ-related toxicities [21].

According to our best knowledge we have presented the first analysis of a series of Polish patients with advanced soft tissue sarcomas treated with trabectedin in clinical practice outside clinical trials. Results of the analysis are similar, both in the response rate and in toxicity profile, to the reports from big multi-centre studies.

Trabectedin is certainly a drug that needs further studies both in monotherapy and also in combination with other chemotherapeutic agents in therapy of advanced soft tissue sarcomas. It is the next promising treatment alternative for this group of patients with poor prognosis after failure of other available standard therapies, especially by demonstrating durable disease control and survival.

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