

Trabectedin for Advanced Soft Tissue Sarcoma: Ten Year Real-Life Perspective

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ABSTRACT: **Background:** Trabectedin is a marine-derived chemotherapy, which has received U.S. Food and Drug Administration approval for use in anthracycline-resistant advanced soft tissue sarcoma (STS), especially liposarcoma and leiomyosarcoma (L-sarcomas).

Objectives: To describe our 10 year real-life experience with trabectedin regarding safety and efficacy in a cohort of 86 patients.

Methods: In our study cohort, 46.51% were diagnosed with liposarcoma and 43.02% with leiomyosarcoma. A total of 703 cycles of trabectedin were given, with a median of five cycles per patient (range 1–59). Median overall survival was 13.5 months for the whole cohort, 11 months for liposarcoma patients (range 1–63), and 15 months for leiomyosarcoma patients (range 1–35).

Results: There was no statistically significant difference in progression free survival when stratified according to previous treatment lines given. Trabectedin exhibited a favorable safety profile, with only 22% requiring dose reductions. Grade 3 and higher toxicity was noted in 25% of the patients, mostly due to myelosuppression. There were no treatment-related deaths.

Conclusions: Trabectedin is a safe and effective drug for treating advanced STS. Our results reflect real-life data with patients receiving the drug as a third and even fourth line of treatment, or with a suboptimal performance status, yet achieving impressive clinical benefit rates and survival.

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KEY WORDS: chemotherapy, leiomyosarcoma, liposarcoma, trabectedin

In the past decade, there have been many developments in the practice of oncology. New therapies have emerged for lung cancer, breast cancer, malignant melanoma, and other malignancies. There have also been a few developments in the field of soft tissue sarcomas (STS). This large heterogeneous family of tumors comprises only about 1% of all adult malignancies [1] while encompassing more than 50 different histological subtypes [2], making it a challenge for cancer research.

One of the few new drugs active against this disease is trabectedin (Yondelis©, Janssen Biotech, Inc. Horsham, PA, USA),

a marine-derived substance that was initially produced from *Ecteinascidia turbinata* [3]. Numerous anti-tumor mechanisms have been identified, among them the ability to form a covalent bond to amino acids in the minor groove of DNA, leading to double-strand DNA breaks, inhibition of nucleotide excision repair pathway, and inhibition of active transcription [4].

Several key trials have demonstrated trabectedin's effectiveness in a few subtypes of soft tissue sarcomas, mainly liposarcoma and leiomyosarcoma, after failure of anthracycline-based treatment. Demetri and colleagues [5] showed median overall survival of 13.9 months in a cohort of patients receiving the drug at 1.5 mg/m² every 24 hours. A phase III trial evaluating the effectiveness of trabectedin against dacarbazine in patients with advanced liposarcoma or leiomyosarcoma demonstrated median progression free survival (mPFS) of 4.2 vs. 1.5 months in favor of trabectedin [6]. This result came after pretreatment with several lines of prior systemic treatment, and led the U.S. Food and Drug Administration to approve this drug, 8 years after the European Medicines Agency's approval for the same indication.

We retrospectively investigated the efficacy and clinical outcome of trabectedin in patients with advanced STS treated at our clinic for bone and soft tissue malignancies.

PATIENTS AND METHODS

The medical records of patients with advanced STS who were treated as in-patients at the oncology department at Tel Aviv Sourasky Medical Center from 2007 to 2015 were retrospectively evaluated. All patients who were treated with at least one cycle of trabectedin were included in the present analysis, after providing written informed consent. The study was approved by the local institutional review board (Helsinki committee).

We reviewed data regarding patient clinical characteristics, including but not limited to histology, previous treatments, performance status, and tumor location. Information was gathered regarding efficacy and safety, as well as survival.

Efficacy evaluation was performed every two or three cycles with computed tomography or positron emission tomography-computed tomography scans, and patient response was assessed using criteria set by rules published by Response Evaluation Criteria In Solid Tumors (RECIST).

STATISTICAL ANALYSIS

Descriptive statistics were used to process the available information. The efficacy and safety analysis included patients who had at least one treatment cycle of trabectedin.

Objective response rate (ORR) was calculated as the number of patients who had either a complete or partial response to treatment divided by the number of patients in the whole cohort. Clinical benefit rate (CBR) was calculated as the proportion of patients who did not have disease progression at time of first evaluation.

We conducted a safety analysis on all patients who received at least one dose of trabectedin.

Kaplan–Meier analyses were used to assess patient progression and overall survival.

RESULTS**PATIENTS**

Our study comprised 86 patients who were being treated at our department between March 2007 and December 2015 and who received trabectedin for STS, for a total of 703 courses.

The study included 35 males (40.7%) and 51 females (59.3%). Median age at diagnosis was 55 years (range 24–83 years). Most of the patients (65.1%) had been diagnosed at an early stage, treated with curative intent, and experienced disease recurrence, while 30 patients (34.9%) had metastatic disease at presentation.

The majority of patients had either liposarcoma (46.51%) or leiomyosarcoma (43.02%). Other histologies included synovial sarcoma (5.81%), pleomorphic sarcoma (1.17%), rhabdomyosarcoma (1.17%), leiomyosarcoma of the bone (1.17%), and metastatic meningioma (1.17%).

Median follow up from the first cycle and until death or at last recorded visit was 13 months (range 1–97).

Patient characteristics are summarized in Table 1.

TREATMENT

Trabectedin was given through a central venous catheter at a dose of 1.5 mg/m² for 24 hours on day 1 of each 21 day cycle. Premedication included anti-emetics to prevent moderate emesis risk. Patients received granulocyte-colony stimulating factor as needed.

Trabectedin was most commonly given as a second (46 patients [53.48%]) or third (22 patients [25.58%]) line therapy. Ten patients (11.62%) received it as a first line treatment for metastatic disease, either due to a short disease-free interval from adjuvant doxorubicin-based chemotherapy (six patients) or due to medical conditions prohibiting doxorubicin and ifosfamide administration (four patients). Eight patients were treated after being exposed to more than three prior lines of treatment.

EFFICACY: LIPOSARCOMA

Forty liposarcoma patients received a total of 381 courses, with a median of 5 courses per patient (range 1–59). Median time of treatment was 4 months (range 1–58).

Table 1. Patient clinical characteristics

Characteristic	
Age	
Median, years (range)	55 (24–83)
Gender (%)	
Male	35 (40.7)
Female	51 (59.3)
Histology (%)	
Liposarcoma	40 (46.51)
Myxoid/round cell	20 (23.25)
Pleomorphic	6 (7.05)
Dedifferentiated	8 (9.41)
Well differentiated	5 (5.88)
Missing	1 (1.17)
Leiomyosarcoma	37 (43.02)
Uterine	18 (21.17)
Non-uterine	19 (22.35)
Synovial	5 (5.81)
Other	4 (4.65)
Tumor location (%)	
Lower limb	25 (29)
Upper limb	1 (1.16)
Abdomen/retroperitoneum	32 (37.2)
Uterus	18 (21)
Head and neck	2 (2.32)
Other	8 (9.3)
Trabectedin given as treatment line (%)	
First	10 (11.62)
Second	46 (53.48)
Third	22 (25.58)
Fourth or more	8 (9.3)
ECOG PS at cycle 1 (%)	
0	1 (1.16)
1	62 (72.09)
2	17 (19.76)
3	5 (5.81)
4	1 (1.16)

ECOG = Eastern Cooperative Oncology Group, PS = performance status

Three out of 40 patients (7.5%) received only one treatment due to deteriorated health: two patients due to Eastern Cooperative Oncology Group (ECOG) performance status of 3 or more and one due to patient wishes.

Trabectedin was given as first line in 5 patients (12.5%), second line in 26 patients (65%), and third line in 9 patients (22.5%).

Median overall survival from the first day of trabectedin treatment and until death or last follow-up was 11 months (range 1–63). There was no statistically significant difference in overall survival whether the drug was given as a first, second, or third line of treatment [Figure 1].

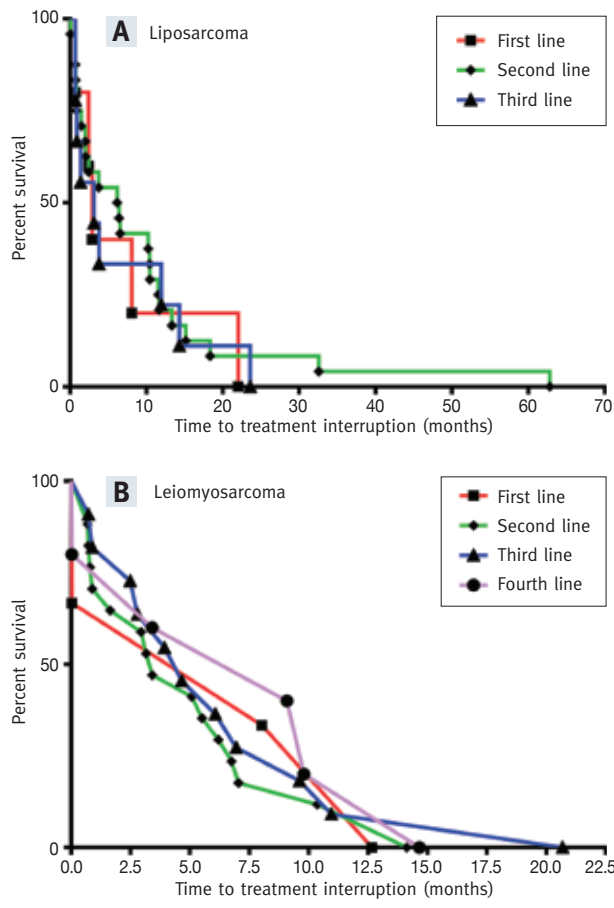
ORR to trabectedin was 15%, with 14 patients (35%) achieving disease stabilization, for a CBR of 50%.

Efficacy data are summarized in Table 2.

EFFICACY: LEIOMYOSARCOMA

In our study, 37 leiomyosarcoma patients received a total of 266 courses, with a median of 6 courses per patient (range 1–25). Median time of treatment was 5 months (range 1–22).

Figure 1. Stratified according to trabectedin timing in relation to other systemic treatments from cycle 1 of trabectedin until the end of treatment **[A]** Survival of liposarcoma patients **[B]** Survival of leiomyosarcoma patients



Three out of 37 patients (8.1%) received only one treatment: two patients due to either deteriorated state or ECOG performance status of 3 or more and one due to toxicity.

Trabectedin was given as first line treatment for 3 patients (8%), second line for 17 patients (46%), and third line for 11 patients (30%). Six patients (16%) were pretreated before receiving the drug.

Median overall survival from the first day of trabectedin and until death or last follow-up was 15 months (range 1–35). There was no statistically significant difference in overall survival whether the drug was given as a first, second, or third line of treatment [Figure 2].

ORR to trabectedin was 32%, with 13 patients (35%) achieving disease stabilization, for a CBR of 67%.

SAFETY

Trabectedin was relatively well-tolerated, with only 19 patients (22%) requiring dose reductions due to toxicity, mainly myelotoxicity or elevated liver function tests.

Table 2. Trabectedin efficacy data

Given as line number	n (%)
First	10 (11.62)
Second	46 (53.48)
Third	22 (25.58)
Fourth and more	8 (9.3)

Response to trabectedin	
Total (n=86)	n (%)
Complete response	2 (2.32)
Partial response	17 (19.76)
Stable disease	28 (32.55)
Progressive disease	18 (20.93)
Mixed response	2 (2.32)
Were not evaluated	19 (22.09)

Liposarcoma (n=40)	n (%)
Complete response	0 (0)
Partial response	6 (15)
Stable disease	14 (35)
Progressive disease	9 (22.5)
Mixed response	2 (5)
Were not evaluated	9 (22.5)
Clinical benefit rate	20 (50)

Leiomyosarcoma (n=37)	n (%)
Complete response	1 (2.7)
Partial response	11 (29.72)
Stable disease	13 (35.13)
Progressive disease	9 (24.32)
Mixed response	0 (0)
Were not evaluated	3 (8.1)
Clinical benefit rate	25 (67.56)

Grade 1–2 toxicity was noted in 66% of cases, mainly myelosuppression and fatigue. Grade 3–4 was noted in 25% of the patients, and included neutropenia (8.13%), anemia (3.4%), thrombocytopenia (5.81%), and elevated liver function tests (5.81%). None of the patients developed neutropenic fever while on treatment. There were no cases of death related to treatment.

Two patients received the drug while on regular dialysis treatments, with no excessive toxicity or schedule interruptions.

Among elderly patients, the treatment was also well tolerated. Ten patients (11.62%) were between 70 and 83 years of age, and they did not exhibit any changes in terms of safety compared with the rest of the cohort.

Safety data are summarized in Table 3.

DISCUSSION

Two recent randomized controlled trials describe the efficacy of trabectedin in anthracyclin-resistant advanced STS. Demetri and co-authors [5] randomized 270 liposarcoma or leiomyosarcoma patients into one of two trabectedin regimens. In that selected group, trabectedin resulted in a median time-to-progression of 3.7 months, ORR was 5.6%, and median overall survival was 13.9 months.

In the second trial, Demetri and colleagues [6] randomized 518 liposarcoma or leiomyosarcoma patients into either trabectedin or dacarbazine. Trabectedin resulted in a superior

Table 3. Trabectedin safety data

Toxicity grade 1–2, n=86 (%)	
Neutropenia	8 (9.3)
Anemia	10 (11.62)
Thrombocytopenia	8 (9.3)
Emesis	8 (9.3)
Weakness and fatigue	15 (17.44)
Elevated liver function tests	5 (5.81)
Constipation	3 (3.48)
Toxicity grade 3–4, n=86 (%)	
Neutropenia	7 (8.13)
Anemia	3 (3.4)
Thrombocytopenia	5 (5.81)
Elevated liver function tests	5 (5.81)
Other	2 (2.32)

mPFS (4.2 vs. 1.5 months), ORR of 10%, duration of response 6.5 months, CBR of 34%, and median overall survival of 12.4 months.

In contrast to these trials, our retrospective data represent real-life experience with trabectedin. We included patients with diverse age, histology, performance status, prior treatments, and tumor burden. The group includes 10 patients (11.6%) who received trabectedin as first line treatment (either due to congestive heart failure or to rapid progression following adjuvant doxorubicin and ifosfamide), 10 patients (11.62%) were older than 70 years of age, 9 (10.5%) had histologies other than liposarcoma or leiomyosarcoma, and 23 (26.7%) had ECOG PS of 2 or higher.

When taking into account these factors, our results of ORR 22%, CBR 54.65%, mPFS of 5.5 months, and median overall survival of 13.5 months, trabectedin showed to be more potent than was expected. It is worth noting that even with a diverse real-life population, the drug was well tolerated.

Other centers have published their retrospective data. Samuels et al. [7] described the results of a worldwide expanded access program from 2005 to 2010. In that cohort, 807 patients had evaluable ORR data for a response rate of 7%. Liposarcoma and leiomyosarcoma patients had median overall survival of 16.2 months, compared to 8.4 months for other histology types.

Gounaris [8], Angarita [9], Hoiczyc [10], Moriceau [11] and their colleagues published retrospective series from their centers (25, 77, 101, and 59 patients, respectively). In a population similar to the one in our cohort, trabectedin resulted in acceptable safety profile with CBR of 24%–60%.

With trabectedin treatment, some patients respond very favorably and for a prolonged time period. In our cohort, 20 patients (23.25%) received more than 10 courses and 7 (8.13%) received more than 20 cycles. Twenty patients (25%) had median overall survival of more than 2 years and in five cases for more than 3 years.

Data are missing for biomarkers and other parameters that could predict clinical benefit from the drug. We know that liposarcomas and leiomyosarcomas respond better than other

histologies, but trabectedin showed efficacy in further subtypes, including synovial sarcomas [12], malignant solitary fibrous tumors [13], and others [14]. In our cohort, the best response was seen with a pleomorphic sarcoma patient who had durable complete response for more than 8 years.

Several phase IV studies on trabectedin have been published during the last years. Buonadonna and colleagues [15] reported mPFS of 5.9 months in 218 patients with STS, 1.4% complete response rate, 25.2% partial response rate, and 39% stabilization rate, which showed a disease control rate of 65.6%, similar to our observation. Stacchiotti and co-authors [16] claimed a limited activity of trabectedin in a cohort of STS. A French trial headed by Le Cesne [17] showed an objective response rate of 17%. Fifty percent of patients had stable disease for a disease control rate of 67%. The mPFS and overall survival were 4.4 and 12.2 months, respectively.

An American group of researchers noted a superior PFS of trabectedin over dacarbazine in uterine sarcoma [18].

CONCLUSIONS

Trabectedin is an effective and highly tolerated treatment modality in anthracycline-refractory STS in all age groups and in various treatment lines. The results of this real-life series demonstrate that treatment with trabectedin of patients with STS yields comparable efficacy outcomes versus those observed in clinical trials and other real-life reports. A long-term treatment regimen with trabectedin is associated with significantly long PFS and overall survival. More data are needed to predict which patients will benefit most.

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Capsule

Foot barriers in patients with early rheumatoid arthritis

Foot impairments are related to reduced mobility and participation restrictions in daily activities in patients with established rheumatoid arthritis (RA). The new biologic medications are effective and reduce disease activity but not disability to the same extent. Foot impairments are assumed to be related to participation restrictions. The same is true in patients with early RA, who were diagnosed after the introduction of biologic medications. Knowledge of foot impairments needs to be explored further after the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs). Bjork et al. explored the patients' perspective of foot impairments related to early RA. The sample included 59 patients (ages 20–63 years) who were interviewed about participation dilemmas in daily life using the critical incident technique. The interviews were audio-recorded and transcribed.

Data related to foot impairments were extracted and analyzed thematically. A research partner validated the analysis. Patients with early RA described a variety of participation restrictions related to foot impairments: foot hindrances in domestic life, foot impairments influencing work, leisure activities restricted by one's feet, struggling to be mobile, and foot impairments as an early sign of rheumatic disease. There is a need to focus on foot impairments related to early RA, and for health-care professionals to understand these signs. A suggestion for future research is to conduct a longitudinal follow-up of foot impairment related to medication, disease activity, and disability in patients diagnosed after the introduction of bDMARDs.

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Capsule

Multinational qualitative research study exploring the patient experience of Raynaud's Phenomenon in systemic sclerosis

Raynaud's phenomenon (RP) is the most common manifestation of systemic sclerosis (SSc). RP is an episodic phenomenon that is not easily assessed in the clinic, and which leads to reliance on self-report. A thorough understanding of the patient experience of SSc-RP is essential to ensuring that patient-reported outcome (PRO) instruments capture domains important to the target patient population. Pauling and colleagues reported the findings of an international qualitative research study investigating the patient experience of SSc-RP. Focus groups of SSc patients were conducted across three scleroderma centers in the United States and England using a topic guide and a priori purposive sampling framework devised by qualitative researchers, SSc patients, and SSc experts. Focus

groups were audio-recorded, transcribed, anonymized, and analyzed using inductive thematic analysis. Focus groups were conducted until thematic saturation was achieved. Forty SSc patients participated in six focus groups conducted in Bath (UK), New Orleans, LA (USA), and Pittsburgh, PA (USA). Seven major themes were identified that encapsulate the patient experience of SSc-RP: physical symptoms, emotional impact, triggers and exacerbating factors, constant vigilance and self-management, impact on daily life, uncertainty, and adaptation. The interrelationship of the seven constituent themes can be arranged within a conceptual map of SSc-RP.

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