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Efficacy of Trabectedin in Patients with Advanced or Metastatic Alveolar Soft-Part Sarcoma

Daniel Pink[a] Janina Bertz-Lepel[a] Christoph Busemann[b] Ulrich Bitz[a] Peter Reichardt[a]

[a]HELIOS Klinikum Bad Saarow, Department of Hematology, Oncology, and Palliative Care, Sarcoma Center Berlin-Brandenburg, Bad Saarow, [b]Internal Medicine C (Hematology and Oncology, Transplant Center), Ernst-Moritz-Arndt-University, Greifswald, Germany

Keywords
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Summary

Background: Alveolar soft-part sarcoma (ASPS) is a rare sarcoma often occurring in young patients that is characterized by the unbalanced translocation der(17)t(X;17)(p11;q25). Although it usually shows an indolent clinical course, the prognosis is usually poor in advanced disease. Since standard chemotherapy regimens used in soft-tissue sarcomas lack efficacy in ASPS, new therapeutic options are needed. We investigated the efficacy of trabectedin, which has demonstrated activity in a variety of cancer types including some of the most prevalent translocation-related sarcomas. **Patients and Methods:** 7 patients with metastatic or advanced ASPS treated with trabectedin in the Sarcoma Center Berlin-Brandenburg and the University Hospital of Greifswald were analyzed for median progression-free survival (mPFS), overall survival (OS), and therapy-related toxicity. **Results:** In 6 patients with documented disease progression, disease stabilization was reached with trabectedin; only 1 patient experienced progressive disease. The mPFS and OS were 7 months and 21 months, respectively, since the start of trabectedin treatment. Overall, no severe Common Toxicity Criteria (CTC) grade 3 or 4 toxicity was observed. **Conclusions:** The poor prognosis of patients with ASPS has so far been due to the unavailability of effective systemic treatments. Trabectedin can be considered the only currently registered drug with clinical activity in this disease.

Schlüsselwörter
ASPS · Trabectedin

Zusammenfassung

Hintergrund: Alveoläre Weichgewebssarkome (ASPS) sind seltene Tumoren häufig junger Patienten, für die eine unbalanzierte Translokation der(17)t(X;17)(p11;q25) charakteristisch ist. Die Prognose der Erkrankung ist trotz ihres meist indolenten Verlaufes häufig schlecht. Da die bei Sarkomen eingesetzten Standardchemotherapien bei ASPS unwirksam sind, werden neue Therapieoptionen benötigt. Wir untersuchten die Wirksamkeit von Trabectedin bei ASPS, da für diese Substanz bei den meisten translokationsassoziierten Sarkomen eine vielversprechende Aktivität nachgewiesen wurde. **Patienten und Methoden:** 7 Patienten mit metastasiertem oder fortgeschrittenem ASPS, die im Sarkomzentrum Berlin-Brandenburg bzw. im Universitätsklinikum Greifswald mit Trabectedin behandelt worden waren, wurden bezüglich ihres medianen progressionsfreien Überlebens (mPFS) und ihres Gesamtüberlebens (OS) sowie therapieassoziierter Nebenwirkungen ausgewertet. **Ergebnisse:** Bei 6 Patienten mit dokumentierter Erkrankungsprogression konnte durch eine Therapie mit Trabectedin eine Erkrankungsstabilisierung erreicht werden, nur 1 Patient war auch unter Trabectedin progredient. Das mPFS und das OS betrugen 7 bzw. 21 Monate ab Beginn der Therapie mit Trabectedin. Es wurden keine schwerwiegenden Therapienebenwirkungen (Common Toxicity Criteria (CTC) 3 oder 4) beobachtet. **Schlussfolgerungen:** Die schlechte Prognose von Patienten mit ASPS wird auch dadurch bestimmt, dass bisher keine effektiven systemischen Therapieoptionen zur Verfügung stehen. Trabectedin ist zurzeit die wohl einzige zugelassene Substanz, die eine klinische Aktivität bei der Behandlung dieser Erkrankung hat.

Introduction

Alveolar soft-part sarcoma (ASPS) is a rare soft-tissue tumor that accounts for approximately 0.5–1% of the soft-tissue sarcomas [1]. Compared to other soft-tissue sarcomas, the disease occurs primarily in younger patients, with a median age at diagnosis between 15 and 35 years [1]. ASPS is associated with an unusual pattern of metastatic spread. For example, brain metastases have been described as a common

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Daniel Pink, M.D.
HELIOS Klinikum Bad Saarow, Department of Hematology, Oncology and Palliative Care, Sarcoma Center Berlin-Brandenburg
Pieskower Straße 33, 15526 Bad Saarow, Germany
Tel. +49 33631 735-27, Fax -28
daniel.pink@helios-kliniken.de

feature of metastatic ASPS whereas they are reported to be relatively unusual with other high-grade sarcomas [2].

ASPS is characterized by the unbalanced translocation der(17)t(X;17)(p11;q25) which results in the fusion *of ASPL* on chromosome 17, a gene of unknown function, to the *TFE3* gene on the X chromosome [3]. Although slow growing, ASPS has a fatal prognosis if complete surgical resection is not possible [4]. In advanced disease, chemotherapy is often used, but unfortunately, because of the rarity of the disease, there are only limited data concerning the response to chemotherapy in patients with ASPS. Up to now it seems that ASPSs are generally much less responsive to any standard chemotherapy than other soft-tissue sarcomas [2, 5].

Trabectedin (ecteinascidin 743 (ET-743); Yondelis®, PharmaMar SA, Madrid, Spain) is a natural marine product isolated from the Caribbean tunicate *Ecteinascidia turbinata.* It covalently binds to the minor groove of DNA, inducing a bend in the double helix toward the major groove [6, 7]. These structural changes are believed to result in the binding of other proteins to the DNA, such as transcription factors and DNA repair proteins [8]. By these mechanisms, trabectedin has been shown to induce lethal double-stranded DNA breaks [9] and G_2/M cell cycle arrest [10].

The promising antineoplastic activity of trabectedin has been demonstrated in a variety of cancer types, including for example ovarian cancer [11], breast cancer [12], liposarcoma and leiomyosarcoma [13]. Interestingly, trabectedin has also shown efficacy in advanced pretreated patients with some of the most prevalent translocation-related sarcomas, such as Ewing's sarcoma [14] or synovial sarcoma [15], supporting the hypothesis that trabectedin might act as a transcription interacting agent.

In some countries, trabectedin is approved for the treatment of advanced soft-part sarcomas after failure of anthracyclines and ifosfamide, or in patients who are unsuited to receive these agents.

As the therapy options for patients with advanced and metastatic ASPS are quite limited and because of the encouraging results in other translocation-related sarcomas, we performed a retrospective analysis to evaluate the efficacy of trabectedin in patients with advanced and metastatic ASPS. Since ASPS often shows an indolent course of disease with unpredictable disease progression, documentation of progression on prior therapies and comparison of progression-free survival (PFS) prior to trabectedin with PFS during trabectedin treatment (growth modulation index (GMI) [16, 17]) is important to evaluate the efficacy of this treatment.

Patients and Methods

Patients

The registries of the Sarcoma Center Berlin-Brandenburg and of the Department of Oncology of the University Hospital of Greifswald were screened for patients with advanced or metastastic ASPS who were treated with trabectedin since 2003. Response to treatment with trabectedin was assessed every 2–3 cycles by computed tomography (CT) scan, applying the response evaluation criteria in solid tumors (RECIST) [18]. Disease progression prior to trabectedin was also evaluated according to RECIST.

Treatment Plan

Trabectedin was given at a dose of 1.5 mg/m^2 as a 24-h continuous intravenous infusion, repeated every 21 days. 2 patients received trabectedin in a reduced dosage because of intensive pretreatment regimens (one at initially 0.9 mg/m^2 and subsequently 1.3 mg/m^2 and the other one at 1.2 mg/m^2). Dexamethasone 4 mg was given orally twice every 12 h the day before and 3 times after treatment, whereas 8 mg were administered intravenously directly before infusion of trabectedin.

Common Toxicity Criteria

The toxicity of trabectedin was evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) scoring system (version 3.0).

Statistical Analysis

PFS was defined as the time from the initiation of treatment to the first documentation of disease progression or death, and overall survival (OS) was defined as the time from the initiation of treatment to death from any cause or loss to follow-up. Both parameters were evaluated using the Kaplan-Meier method. The GMI (PFS2/PFS1) was calculated from the PFS prior to trabectedin treatment (PFS1), i.e. on a previous drug or without therapy, and the PFS on trabectedin (PFS2).

Results

Patients

A total of 7 patients with ASPS were treated with trabectedin in the 2 institutions participating in this retrospective study. The patient characteristics are outlined in table 1. The median age at primary diagnosis was 28 years (range 15–70 years). There were 4 female and 3 male patients. The majority of primary tumors were located at the lower extremities. 5 of

Table 1. Patient characteristics

Patient	Gender	Age at primary diagnosis, years	Site of primary tumor	Site of metastasis at the time of diagnosis	Previous chemotherapy
A	M	35	left buttock	lung, lymph nodes	yes
B	F	20	right lower leg	lung, bone	no
C	M	70	right groin	lung, liver	yes
D	F	45	right thigh	lung, bone, brain	yes
E	M	28	right upper arm	–	yes
F	F	23	left buttock	lung, bone	yes
G	F	15	left thigh	–	yes

Table 2. Prior therapies

Patient	Previous surgery	Previous radiotherapy	Previous chemotherapy	Lines of prior chemotherapies	Drugs
A	yes	yes	yes	4	doxo/ifos, MTX/cisplatin, interferon α2b, trofosfamide
B	no	no	no		
C	yes	yes	yes	1	experimental drug
D	yes	yes	yes	3	doxo/dacarbazine, trofosfamide, interferon α2b
E	yes	no	yes	2	cyclo/doxo/dacarbazine, doxo/ifos
F	yes	yes	yes	2	doxo/ifos, topotecan/carboplatin
G	yes	yes	no		

doxo = Doxorubicine, ifos = ifosfamide, MTX = methotrexate, cyclo = cyclophosphamide.

Table 3. Response and survival

Patient	PFS1, months	Treatment cycles	PFS2, months	PFS2/PFS1	OS since beginning of therapy with trabectedin, months	OS since first diagnosis of metastasis, months
A	3	10	7	3.33	7	37
B	n.a.	19	12	n.a.	40	40
C	2	8	5	2.5	13+	15+
D	2	5	3	1.5	4	58
E	5	17	20	4	21	42
F	4	23	15	3.75	29+	42+
G	3	4	4	1.33	13+	16+

PFS1 = Progression-free survival before therapy with trabectedin, PFS2 = progression-free survival with trabectedin, OS = overall survival, n.a. = not applicable.

7 patients presented with primarily metastatic disease, with the most common sites of metastasis being lung (5/5) and bone (3/5). Only 2 of the patients had not been pretreated with chemotherapy (table 2).

All but 1 patients had documented disease progression prior to starting treatment with trabectedin. 1 patient with newly diagnosed symptomatic metastatic ASPS was treated with trabectedin as first-line therapy. The median time between diagnosis of ASPS and initiation of treatment with trabectedin was 15 months (range 0–55 months). The median number of treatment cycles was 10, ranging from 4 to 23 cycles.

Response/Survival

Among the 7 patients treated with trabectedin, 6 experienced stable disease (SD) according to RECIST criteria as best response for at least 3 months (86%), and there was 1 progressive disease (PD) (14%). After 6 months of treatment, the progression-free rate constituted 57%.

The median PFS was 7 months (range 3–20 months), with no patient still continuing treatment with trabectedin. 3 patients died and 1 was lost for follow-up.

The GMI was 1.33 in 1 patient and >1.33 in 5 patients. 1 patient was not evaluable for GMI since treatment with trabectedin was started immediately after diagnosis of metastatic ASPS.

The OS with trabectedin is 21 months (range 4–40 months) and the median survival since the first diagnosis of metastases was 42 months (range 15+ to 58 months). The median follow-up/OS since primary diagnosis of ASPS was 46 months (range 15+ to 58 months) with 3 of the 7 patients being alive at their last follow-up (15+, 16+ and 45+ months) (table 3).

Toxicity

All patients underwent regular clinical and laboratory assessment to evaluate the treatment toxicity. An elevation of transaminases CTC grade 1–3 was detected in all cases, but spontaneous recovery before the next treatment cycle occurred in all patients so that no dose reduction or discontinuation of treatment had to be performed. Hematological toxicity was seen as 1 leukopenia CTC grade 2 and 1 thrombocytopenia CTC grade 1. Only 1 patient reported about nausea/vomiting CTC grade 1, and 2 patients experienced fatigue CTC grade 1 and 2, respectively. Overall, no severe CTC grade 3 or 4 toxicity was observed.

Discussion

ASPS is a rare subentity of soft-tissue sarcomas and is generally much less responsive to any standard chemotherapy than other soft-tissue sarcomas. Overall response rates to conventional doxorubicin-based chemotherapies of approximately 7% have been reported [2].

New promising data about compounds active in advanced or metastatic ASPS have been fully published or presented at the American Society of Clinical Oncology (ASCO) annual meetings 2009/2010. Palassini et al. [19] reported about the activity of the multi-tyrosine kinase inhibitor sunitinib malate in 8 patients with ASPS. 5 partial responses (PR) and 1 SD could be achieved with long-lasting responses and the opportunity of reinduction of responses when restarting therapy with sunitinib after progression of the disease in a treatment-free interval. Another promising potential therapeutic option could be cediranib, a highly potent and selective vascular

epithelial growth factor (VEGF) signaling inhibitor, which induced PR as best response in 4 of 7 patients treated [20]. Furthermore, ARQ 197, a selective, non-ATP-competitive inhibitor of c-Met, also seems to be active in ASPS and other microphthalmia transcription factor family (MiT)-associated tumors, with a disease control rate of 80% in 20 patients [21].

In this retrospective study, we analyzed the efficacy of trabectedin in 7 patients with advanced or metastatic ASPS. As all but 1 patient had documented disease progression before starting therapy with trabectedin, the median PFS of 7 months can clearly be attributed to an antiproliferative effect of trabectedin instead of being a result of the slow-growing nature of this disease, although in rare cases spontaneous regression or disease stabilization have been described in the literature [22].

In 6 out of 7 patients, the GMI was ≥ 1.33, a cut-off considered to indicate activity of a treatment modality [16]. 1 patient was not evaluable.

As no severe CTC grade 3 or 4 toxicities were seen, treatment with trabectedin can be considered as a fairly well-tolerated therapy option. Further, it can be considered the only approved treatment option for which an efficacy in ASPS has been demonstrated.

In conclusion, the therapy of metastatic or advanced ASPS remains difficult. New promising therapeutic options are given with sunitinib, cediranib and ARQ 197, but further studies are needed to evaluate the efficacy and long-term results of these compounds. Up to then, trabectedin can be considered as a fairly well-tolerated therapy option to achieve disease stabilization in patients who have experienced disease progression.

Disclosure Statement

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