The value of trabectedin in the treatment of soft tissue sarcoma

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Abstract: Soft tissue sarcomas (STSs) are a group of rare tumors accounting for less than 1% of all adult malignant tumors, a heterogeneous group of more than 50 histological subtypes. Five percent to 30% of STS patients experience local recurrence and 10%–38% present with clinically detectable metastases. Doxorubicin either alone or in combination with ifosfamide has been used as first-line chemotherapy for advanced disease. After failure of first-line chemotherapy, high-dose ifosfamide, gemcitabine + docetaxel, and dacarbazine may be applicable, although high-level evidence is lacking. Trabectedin is a synthetic, marine-derived alkylating agent derived from the Caribbean tunicate, *Ecteinascidia turbinata*. Several clinical trials have shown that trabectedin has a favorable toxicity profile and is an alternative therapeutic option in adult patients with advanced STS who have not responded to treatment with doxorubicin and ifosfamide. Several clinical trials also recommend the 24-hour intravenous infusion every 3 weeks regimen. The most frequently reported grade 3/4 adverse events were neutropenia and elevated serum levels of AST/ALT. Steroid pretreatment is an effective way of reducing the extent of hepatotoxicity, and steroids are now given routinely before trabectedin administration. Further studies are ongoing to evaluate the efficacy and safety of combination therapy of trabectedin with other agents.

Keywords: trabectedin, soft tissue sarcoma, efficacy, safety

Introduction

Soft tissue sarcomas (STSs) are a group of rare solid tumors accounting for less than 1% of all adult malignant tumors and 4%–8% of childhood malignancies, a heterogeneous group of more than 50 histological subtypes.[1–5] Surgical resection with or without adjuvant radiotherapy is the standard treatment of all patients with an adult type, localized STS.[4–9] Adjuvant chemotherapy may additionally be considered in the localized setting, however, its role in management remains controversial.[4] Five percent to 30% of STS patients experience local recurrence and 10%–38% present with clinically detectable metastases.[9–13] Complete surgical resection is reportedly a pivotal therapeutic option to provide patients with prolonged survival.[4,14] However, even after a seemingly complete resection of metastatic tumors, metastasis will recur in 40%–80% of the patients.[15] Systemic therapy for advanced disease is another therapeutic option in the management of metastases.[4,16–21] Over the previous decades, doxorubicin either alone or in combination with ifosfamide has been used as first-line chemotherapy, however, it has not greatly improved the patient's prognosis.[4,16–21] Although standard chemotherapy was performed, the median survival time is 8 to 13 months from initiation of first-line chemotherapy.[17–21] After failure of standard chemotherapy, high-dose ifosfamide,[22,23] gemcitabine + docetaxel,[24] and dacarbazine[25] may be applicable, although high-level evidence is lacking. Recently a randomized

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Phase III trial (PALETTE) of pazopanib treatment for advanced STS after failure of conventional chemotherapy demonstrated the potential benefit of pazopanib for a prolonged progression-free survival (PFS).[26] Trabectedin is a synthetic, marine-derived alkylating agent derived from the Caribbean tunicate, *Ecteinascidia turbinata*.[27,28] The success of trabectedin in preliminary clinical trials for STSs has led to the approval of the drug in European countries in 2007 for the treatment of patients with advanced STS after the failure of therapy with doxorubicin either alone or in combination with ifosfamide. With limited systemic therapy options available as a whole, trabectedin has the opportunity to be significantly beneficial for patients with STSs. The purpose of this review is to summarize the efficacy and toxicity of trabectedin in the treatment of STS.

Each author certifies that his institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with the ethical principles of research.

Mechanism of trabectedin

Trabectedin is a tetrahydroisoquinoline alkaloid derived from the Caribbean marine tunicate, *Ecteinascidia turbinata*, and is currently produced synthetically.[27,28] Trabectedin interacts with the minor groove of DNA double helix and alkylates guanine at the N2 position, which bends toward the major groove,[29–31] triggering a cascade of events that interferes with several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in G2 – M cell cycle arrest and ultimately apoptosis.[29] Furthermore, the pattern of sensitivity observed in cells deficient in DNA repair mechanisms is different. In the case of trabectedin, nucleotide excisional repair and homologous recombination repair are of particular importance.[29,32–34] In contrast to other DNA-damaging agents such as cisplatin, nucleotide excisional repair-deficient cells are two to ten times less sensitive to trabectedin.[35] On the other hand, cells deficient in homologous recombination repair are sensitive to trabectedin. Nevertheless, emerging evidence indicates that trabectedin has pleiotropic mechanisms of action, since, in addition to direct growth inhibition, cell death, and differentiation of malignant cells, trabectedin at therapeutic concentrations has selective immunomodulatory properties as a result of the inhibition of the production of factors that promote tumor growth, progression and inhibition of tumor-promoted angiogenesis. Trabectedin selectively targets monocytes and tumor associated macrophages and downregulates the production of inflammatory mediators such as IL-6 and CCL2, which may

underlie the strong association between chronic inflammation and cancer progression.[31,36]

Trabectedin also has a specific mechanism against some translocation-related sarcomas. Recent investigations have demonstrated that trabectedin blocks the trans-activating ability of chimaeras by displacing the oncogenic fusion protein FUS-CHOP from its target promoters.[37,38] This eventually induces adipogenic differentiation of myxoid liposarcoma cells. This effect has been observed in FUS-CHOP expressing experiment models and tumor biopsies taken before and after trabectedin therapy in patients with myxoid liposarcoma.[37,39]

Efficacy of trabectedin for advanced STSs

Two Phase II trials in 2004 provided the initial analysis of trabectedin in STSs (Table 1).[40,41] Trabectedin was administered at a dose of 1.5 mg/m², 24-hour intravenous (IV) infusion every 3 weeks (q3ws). The first of these studies was conducted in 54 advanced or metastatic STS patients with disease progression despite prior chemotherapy.[40] The objective response rate was 4%, however, the disease control rate at 6 months was 24%. The median PFS and overall survival (OS) were 1.9 months and 12.8 months, respectively. The second Phase II trials reported a low response rate of 8% in 36 recurrent or metastatic STS patients with disease progression despite prior chemotherapy.[41] The median PFS and OS were 1.7 months and 12.1 months, respectively. In a small series of chemotherapy naïve patients, a 17.1% response rate with a 16.5-month median PFS was reported. Recently, results from randomized, multicenter, prospective dose-selection Phase IIb trials to evaluate whether trabectedin as first-line chemotherapy for advanced/metastatic STS prolongs the PFS, compared to doxorubicin, were published.[42] One hundred and thirty-three patients were randomized (1:1:1) to doxorubicin, trabectedin (3-hour [T3h arm] infusion q3ws), or trabectedin (24-hour [T24h arm] infusion q3ws). The median PFS was 2.8 months in the T3h arm, 3.1 months in the T24h arm, and 5.5 months in the doxorubicin arm. No significant improvement in the PFS was observed in the trabectedin arms as compared to the doxorubicin arm (T24h vs doxorubicin: hazard ratio [HR] 1.13; 95% confidence interval [CI] 0.67–1.90, *P*=0.675; T3h vs doxorubicin: HR 1.50, 95% CI 0.91–2.48, *P*=0.944). The authors concluded that doxorubicin continues to be the standard treatment in eligible patients with advanced/metastatic STS as first-line treatment.

The efficacy of trabectedin 1.5 mg/m² 24-hour IV infusion q3ws in patients with pretreated advanced or metastatic

Table I Clinical trials of trabectedin (Phase II and III)

Study design	Patients	Regimen	ORR	Median	
				PFS	**OS**
Phase II[44]	LPS or LMS	A; T 1.5 mg/m² 24-h q3ws	5.6%	3.7 mos	13.9 mos
R (1:1)	n=270	B; T 0.58 mg/m² 3-h weekly	1.6%	2.3 mos	11.8 mos
Phase II[41]	STS	T 1.5 mg/m² 24-h q3ws	8%	1.7 mos	12.1 mos
	n=36				
Phase II[65]	STS	T 1.5 mg/m² 24-h q3ws	8%	3.4 mos	9.2 mos
	n=104				
Phase II[42]	STS	A; T 1.3 mg/m² 3-h q3ws	14.8%	2.8 mos	
R (1:1:1)	n=133	B; T 1.5 mg/m² 24-h q3ws	4.7%	3.1 mos	
		C; D 75 mg/m² q3ws	25.6%	5.5 mos	
Phase II[40]	STS	T 1.5 mg/m² 24-h q3ws	4%	1.9 mos	12.8 mos
	n=54				
Phase III[46]	LPS or LMS	A; T 1.5 mg/m² 24-h q3ws	9.9%	4.2 mos	12.4 mos
	n=518	B; Dac 1 g/m² 20- to 120-minute q3ws	6.9%	1.5 mos	12.9 mos
Phase II[49]	T-STS	A; T 1.2 mg/m² 24-h q3ws	11%	5.6 mos	Not reached
R (1:1)	n=76	B; Best supportive care	0%	0.9 mos	8 mos
Phase III[55]	T-STS	A; T 1.5 mg/m² 24-h q3ws	5.9%	16.1 mos	
R (1:1)	n=121	B; D 75 mg/m² q3ws or D 60 mg/m² +I 6–9 g/m² q3ws	27%	8.8 mos	
Phase II[53]	STS	1.5 mg/m² 24-h q3ws	2.5%		
	n=40				

Abbreviations: R, randomized study; STS, soft tissue sarcoma; A, group A; B, group B; C, group C; T, trabectedin; D, doxorubicin; I, ifosfamide; Dac, dacarbazine; q3ws, every 3 weeks; h, hour; ORR, objective response rate according to Response Evaluation Criteria In Solid Tumors criteria; PFS, progression-free survival; OS, overall survival; mos, months; LPS, liposarcoma; LMS, leiomyosarcoma; T-STS, translocation-related soft tissue sarcoma.

STS was previously evaluated in non-randomized Phase II studies.[40–42] A weekly trabectedin schedule (0.58 mg/m² 3-hour IV infusion for 3 consecutive weeks in a 4-week cycle) was demonstrated to have substantial anticancer activity in pre-treated ovarian cancer.[43] To assess the efficacy and safety of these two schedules in STS, a randomized, open-label, Phase II trial was conducted in patients with advanced and/or meta-static liposarcomas or leiomyosarcomas after the failure of standard therapies.[44] The time to progression was the primary endpoint. The 24-hour IV q3ws demonstrated a superior time to progression of 3.7 months vs 2.3 months (HR, 0.734; 95% CI, 0.554–0.974; P=0.0302). The median PFS was 3.3 months vs 2.3 months (HR, 0.755; 95% CI, 0.574–0.992; P=0.0418). The median OS was 13.9 months vs 11.8 months (HR, 0.843; 95% CI, 0.653–1.090; P=0.1920). The authors concluded that these data recommend 24-hour IV q3ws regimen. Recently, other Phase II trials showed a similar conclusion that the 1.5 mg/m²/24-hour IV infusion is the optimal approach to delivering trabectedin in the second-line setting.

Due to treatment-related toxicities, most sarcoma experts often propose a drug holiday followed by re-challenge at pro-gression. However, the effect of this approach remains unclear, because no evidence has indicated the absence of deleterious effects of trabectedin discontinuation in non-progressive patients. Therefore, to elucidate the benefit or harm of tra-bectedin discontinuation in patients with non-progression, a Phase II trial investigating the clinical benefit of continua-tion of trabectedin treatment (1.5 mg/m² 24-hour IV infusion q3ws) until progression vs the interruption of therapy after six cycles in patients with advanced STS was performed.[45] Fifty-three patients were randomly assigned to two groups: 27 to the continuation group and 26 to the interruption group. After randomization, the PFS at 6 months was 51.9% (95% CI, 31.9–68.6) in the continuation group vs 23.1% (95% CI, 9.4–40.3) in the interruption group (P=0.02). The authors con-cluded that trabectedin discontinuation in patients with non-progressive disease is not recommended. Recently, trabectedin has been approved by the US Food and Drug Administration (FDA) based on the result of an open-label, randomized (2:1) Phase III trial of trabectedin (n=345) vs dacarbazine (n=173) in patients with metastatic liposarcoma or leiomyosarcoma.[46] In the final analysis of PFS, trabectedin administration resulted in a 45% reduction in the risk of disease progression or death compared with dacarbazine. The median PFS was 4.2 months vs 1.5 months (HR, 0.55; 95% CI, 0.44–0.70; P<0.001).

It has been reported that translocation-related sarcoma responds well to trabectedin treatment. Trabectedin has shown particular activity in myxoid liposarcoma. In a multicenter,

retrospective analysis of 51 patients, a median overall response rate of 51% was reported, and the median PFS was 14 months.[47] The PFS at 6 months was also reported to be 88%. In another study assessing the efficacy of trabectedin in specific translocation-related sarcomas, the PFS at 6 months was 64%.[48] A recent Phase II study in the second-line setting or later has been reported.[49] This study was a randomized Phase II study of trabectedin monotherapy vs supportive care in patients with translocation-related sarcoma subtypes. The patients were randomized (1:1) to receive trabectedin (1.2 mg/m² 24-hour infusion q3ws) or best supportive care. The trabectedin dose of this trial was 1.2 mg/m² according to the results of a Phase I study in Japanese patients with STSs, in which two of three patients had dose-limiting toxicity at 1.5 mg/m².[50] The primary endpoint of this trial was the PFS. The median PFS of the trabectedin group was 5.6 months and that of the best supportive care group was 0.9 months (HR, 0.07; 95% CI, 0.03–0.16; $P<0.0001$). The authors concluded that trabectedin could present a novel treatment option for patients with translocation-related sarcoma who did not respond to doxorubicin-based chemotherapy. The success of trabectedin in this clinical trial for STSs has led to the approval of the drug in Japan. Modulation of transcription by trabectedin has also been shown in Ewing's sarcoma, which is driven by the oncogenic fusion gene *EWS-FLI1*.[51,52] However, a Phase II trial in children with recurrent STS, including Ewing's sarcoma, showed that trabectedin did not demonstrate sufficient activity as a single agent.[53] Of eleven patients with Ewing's sarcoma in the Phase II component, only one patient achieved stable disease (SD) after four cycles. The other nine patients had progressive disease.[53] Recently, it has been shown that this modulation can be exploited to select a very effective combination treatment of trabectedin followed by irinotecan.[54] An observational study of combination treatment of trabectedin followed by irinotecan for refractory pediatric sarcoma is currently ongoing (ClinicalTrials.gov Identifier; NCT 02509234). The purpose of this study is to determine if this is a promising treatment option with acceptable toxicity and if the results warrant a prospective study.

One Phase III study in the first-line setting has been reported.[55] This study was a randomized, Phase III study of first-line trabectedin vs doxorubicin-based chemotherapy in patients with translocation-related sarcoma subtypes.[55] The primary endpoint of this trial was the PFS. Patients were randomized (1:1) to receive trabectedin (1.5 mg/m² 24-hour IV infusion q3ws), doxorubicin 75 mg/m² IV q3ws, or doxorubicin 60 mg/m² IV plus ifosfamide (range, 6–9 g/m²)

IV q3ws. There was no difference in the median PFS or OS between the groups ($P=0.9573$ and $P=0.3659$, respectively). The response rate according to the RECIST (Response Evaluation Criteria In Solid Tumors) criteria was significantly higher in the chemotherapy arm (27%) compared to the trabectedin arm (5.9%). In contrast, the response rate according to the Choi criteria showed fewer differences between the chemotherapy arm (45.9%) and trabectedin arm (37.3%).

Role of trabectedin for neoadjuvant therapy

One Phase II clinical trial in the neoadjuvant setting in patients with advanced localized myxoid liposarcoma has been previously reported.[56] The treatment consisted of trabectedin 1.5 mg/m² given as a 24-hour IV infusion q3ws. Twenty-nine patients received a minimum of three and a maximum of six cycles before surgery. Of 23 patients who could be evaluated by the pathological response, three patients achieved a pathological complete response. Another 12 of 23 had at least a good regression rate (>50% regression). Of 29 patients, seven patients (24%) had a partial response and 21 patients had SD according to the RECIST criteria. One patient died prior to the evaluation due to rhabdomyolysis with hepatic and renal failure after the second trabectedin cycle. The authors concluded that trabectedin is a therapeutic option in the neoadjuvant setting of myxoid liposarcoma. A Phase I–II study that combines trabectedin plus radiotherapy for patients with myxoid liposarcoma and metastatic STS is currently recruiting participants (ClinicalTrials.gov Identifier; NCT 02275286). The study is testing the hypothesis that administering trabectedin plus radiotherapy shows synergic activity that turns into tumor shrinkage. A Phase III study currently enrolling patients is comparing the impact of standard neoadjuvant chemotherapy (epirubicin and ifosfamide) with that of neoadjuvant therapy tailored to the specific histology on the disease-specific survival (ClinicalTrials.gov Identifier; NCT 01710176); patients with leiomyosarcoma or myxoid liposarcoma with round cell liposarcoma will receive gemcitabine plus dacarbazine or trabectedin, respectively.

Safety

Trabectedin was well tolerated in a retrospective pooled analysis of five Phase II trials.[57] The data collected from 350 adult patients were divided into the younger (<60 years; n=267) and the older cohort (≥60 years; n=83). The most frequently reported grade 3/4 adverse events were

neutropenia (47.6%) and elevated serum levels of AST/ALT (44.6%/34.4%). Some grade 3/4 adverse events were more common in patients aged ≥60 years compared to patients <60 years, namely anemia 10.1% vs 19.3%, neutropenia 43.6% vs 60.2%, thrombocytopenia 11.3% vs 20.5%, and fatigue 6.4% vs 14.5%, respectively. Deaths associated with drug-related adverse events were infrequent (1.9% and 2.4% of the patients in the younger and older cohorts, respectively). This pooled analysis also showed similar response rates (10.1% and 9.6% of the patients in the younger and older cohorts, respectively), no significant difference in the median PFS (2.5 months vs 3.7 months, respectively) and similar OS rates between the two cohorts (13.0 months vs 14.0 months, respectively). Other trials showed a similar rate of severe neutropenia, while the standard first-line agents in STSs, doxorubicin and ifosfamide, induced substantially more severe hematological toxicities. Randomized trials with doxorubicin showed grade 3/4 neutropenia in 77% of the patients, with 16%–19% febrile neutropenia, and high-dose ifosfamide caused neutropenia and infection in 20% and 4% of the patients, respectively.[19,44,58] Transaminase increase was the most frequent cause of dose reductions. However, the occurrence of hepatobiliary adverse events was low, further supporting the observation that the liver dysfunction induced by trabectedin is mostly transient, non-cumulative, and without clinical consequences.[44,57,59] A recurring pattern was observed with increased transaminase levels, typically reaching a peak between days 5 and 7 of each cycle and resolving to grade ≤1 by day 15 without implication for the patient.[35] Steroid pretreatment is an effective way of reducing the extent of hepatotoxicity, and steroids are now given routinely before trabectedin administration. Premedication with 20 mg of dexamethasone IV 30 minutes prior to trabectedin was shown to provide hepatoprotective effects beyond its antiemetic effect.[59–61] Although extremely rare, trabectedin-associated rhabdomyolysis is considered to be a potential adverse event. The incidence appears to be approximately 0.5% in patients with sarcoma and ovarian cancer.[62] Elevations in creatine kinase are observed, however, the incidence of muscle damage is low. No predictive factors have been identified to prospectively identify patients who may be at risk of rhabdomyolysis, and therefore, careful clinical and biochemical monitoring is mandatory at each cycle.

Combination therapy of trabectedin with other agents

Combination therapy of trabectedin with other chemotherapeutic agents has been assessed in Phase I trials. The most promising results in sarcoma patients have been from the trials administering trabectedin in combination with doxorubicin.[63,64] One of the trials showed a response rate of 18% and SD in 56% of 29 patients with STS. Another study assessing combination therapy with doxorubicin reported a response rate of 12% with a median PFS of 9.2 months for 41 patients, including 20 liposarcomas and eleven leiomyosarcomas.

Conclusion

Trabectedin has shown a favorable toxicity profile and is an alternative therapeutic option in adult patients with advanced STS who have not responded to treatment with doxorubicin and ifosfamide. Several clinical trials recommend the 24-hour IV q3ws regimen. Furthermore, trabectedin discontinuation in patients with non-progressive disease is not recommended. Steroid pretreatment is an effective way of reducing the extent of hepatotoxicity, and steroids are now given routinely before trabectedin administration. Further study is ongoing to evaluate the efficacy and safety of combination therapy of trabectedin with other agents.

Disclosure

Each author certifies that he has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements) that might pose a conflict of interest in connection with the submitted article.

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