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EXPERT REVIEW

Management of Ovarian Cancer and Soft Tissue Sarcoma: Focus on Trabectedin

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Abstract: Ovarian cancer (OVCA) and soft tissue sarcoma (STS) are cancers that cause low survival rates when diagnosed at advanced disease stage and patients with these cancers usually suffer from recurrent disease. Trabectedin, an alkaloid of marine origin has recently demonstrated improvement in managing advanced recurrent OVCA and STS. It is currently approved as a single therapeutic agent for second line therapy of STS in the USA and Europe. It is also approved in combination with pegylated liposomal doxorubicin as a second line therapy for OVCA in Europe. This review summarizes recent clinical data demonstrating the efficacy of using trabectedin as a second line therapy in OVCA and in STS.

Keywords: trabectedin, ovarian cancer, soft tissue sarcoma, recurrence, chemotherapy, combination

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Introduction

Ovarian carcinoma and soft tissue sarcomas are two types of cancer that suffer from recurrence and cause poor patient prognosis when detected at an advanced stage. Ovarian cancer (OVCA) is the leading cause of death from gynecologic malignancy, and this is a direct outcome of its late initial diagnosis in addition to recurrence of OVCA that is associated with resistance to therapy.[1–4] Approximately 75% of OVCA patients are initially diagnosed with disseminated intra-abdominal disease (stage III–IV) by which stage only 35% of stage III and 17% of stage IV patients survive for 5-years.[5] Treatment for OVCA usually involves cytoreductive surgery followed by the standard first line chemotherapeutic combination regimen of platinum- and taxane-based drugs such as carboplatin (or cisplatin) with paclitaxel.[6–8] Nevertheless, most of the patients will eventually undergo relapse of OVCA.[6,8]

Soft tissue sarcomas (STS) are rare malignant tumors that arise in soft connective or supportive tissue such as adipose tissue, muscles, tendons, nerves, and blood and lymph vessels. In the USA the 5-year survival rate for STS is 90% for stage I patients, whereas it is only 10%–20% for stage IV disease.[9] The treatment of STS may involve surgery with or without radiation; or for advanced disease, treatment involves chemotherapy with doxorubicin and/or ifosfamide.[9–12] STS has the propensity for recurrence which may be hard to treat and can lead to poor prognosis.[9,13]

Trabectedin is a chemotherapeutic agent that has recently been evaluated for efficacy with both OVCA and STS as a second-line treatment, and promising results earned it approval for treatment of these two cancers in Europe and approval for treating STS in the USA. This review focuses on recent literature from 2005 till today and describes trabectedin's mechanism of action, metabolism and pharmacokinetics, and its efficacy in treating OVCA and STS as a single agent or in combination with other chemotherapeutic agents. Literature search was performed in Embase and PubMed from 2005 to date using the search terms "trabectedin, ET-743 or Yondelis" and "sarcoma or ovarian cancer", and the search was limited to English language results.

Mechanism of Action of Trabectedin

Trabectedin is an alkaloid of marine origin with a structure made of three fused tetrahydroisoquinoline rings (Fig. 1). It is also referred to as Yondelis, Ecteinascidin 743, or ET 743 and it is produced through chemical synthesis for use as a chemotherapeutic agent. Its chemical formula is C_{39} H_{43} N_3 O_{12} S and it has a molecular weight of 777.

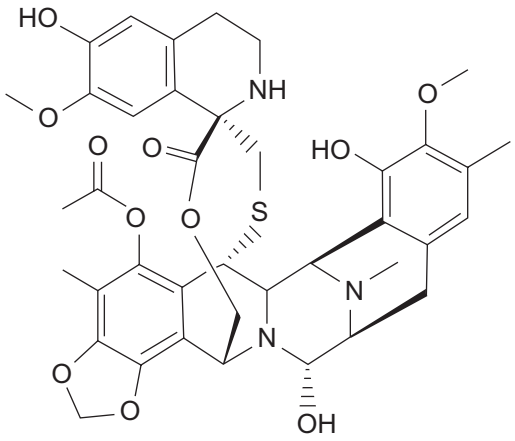

Figure 1. Structure of trabectedin.

Trabectedin is unique in that a number of mechanisms of action may contribute to its anticancer properties. First of all trabectedin interacts with DNA and acts as an alkylating agent through binding to the exocyclic N2 amino group of guanine in specific DNA sequences (5′-PuGC, and 5′-PyGG) in the minor groove[14] causing bending of the DNA towards the major groove.[15,16] Interestingly, the formed DNA adducts create specific DNA structures that bind to zinc finger transcription factors[17] resulting in alteration of transcriptional gene regulation. Trabectedin affects the DNA binding activity of several well-characterized DNA binding proteins including E2F, SP-1, TBP (TATA binding protein), SRF, and NF-Y.[18–20] Importantly, trabectedin did not globally inhibit DNA binding or trasactivation of transcription factors.[18–20] The studies on trabectedin's role in modulating gene transcription are limited. However the current data suggest that part of the mechanism of action for trabectedin is by interfering with oncogenic transcription factors. For example, E2F, Sp-1, and SRF (serum response factor) have all been implicated in ovarian cancer[21–23] and NF-Y (nuclear transcription factor Y) may also play a role in ovarian cancer chemoresistance.[24]

The effect of trabectedin on NF-Y mediated transcription has been studied in a little more depth. Trabectedin selectively inhibits NF-Y DNA binding activity.[25] Furthermore it has been demonstrated that NF-Y activates the multi-drug resistance gene

(MDR1) and trabectedin inhibits this activation.[20] One of the results of this interference is failure of MDR1 upregulation, which may lead to a more sustained response to chemotherapy.

In addition to generating DNA adducts, trabectedin affects other cellular processes. First, the effectiveness of trabectedin requires intact nucleotide excision repair (NER) and homologous recombination (HR) pathways.[26,27] In mammalian cells trabectedin treatment increased double strand breaks (DSB) (as seen by Rad51 and gamma-H2aX foci) whereas cells lacking NER (due to deficiency in ERCC1), showed no increase in DSB in response to trabectedin.[27] This supports the idea that NER is required for trabectedin induced toxicity. Knowing if a particular patient has intact NER pathways, may predict their response to trabectedin therapy. Expression of BRCA1, ERCC1, XPG may also be predictive of a patient's likelihood to respond to trabectedin.[28,29] Hereditary ovarian cancer occurs in about 10% of patients.[30] Of this 10% approximately 90% have mutations in BRCA1 or BRCA2.[30] Other studies suggest that about 10% of ovarian cancer patients carry germline BRCA1/2 mutations.[31] Therefore, trabectedin treatment is not likely to be effective on most patients with hereditary ovarian carcinoma. Genetic screening or expression analysis for proteins in HR and NER pathways would be beneficial prior to recommending trabectedin treatment. The likelihood of response to trabectedin is higher in patients with low BRCA1 expression, ie, patients with deficiency in homologous recombination repair, whereas it is lower in patients with low XPG Expression, ie, in patients with intact excision repair.[32] Thus examination of the levels of these genes may have prognostic value.

Another interesting function of trabectedin is specific to myxoid liposarcomas (MLS) which are very sensitive to trabectedin.[33,34] These MLS tumors possess a translocation at t(12;16)(q13;p11).[35] The rearrangement generates a fusion between the genes FUS and CHOP (called FUS-CHOP, which is an oncogene). CHOP is a member of the C/EBP family of transcription factors that are involved in adipocyte differentiation.[36] Treatment of MLS cell lines with trabectedin interferes with binding of FUS-CHOP oncogene to its target genes and induces adipocyte differentiation.[37]

Other affects of trabectedin include targeting topoisomerase I to induce DNA strand breakage[38] and causing changes in inflammation, cell cycle arrest, and apoptosis. Trabectedin induced apoptosis in human blood monocytes, and tumor associated macrophages (TAMs) in ovarian cancer patients and decreased CCL2 and IL-6 production.[39,40] Treatment of monocytes with trabectedin inhibited macrophage differentiation.[39] Trabectedin also inhibited cytokine production in MLS tumor cultures and cell lines.[40] Trabectedin was demonstrated to induce cell cycle arrest (dependent on gene transcription) and apoptosis that does not rely on transcription but requires mitochondria, JNK (c-jun kinase), and caspase 3 activities.[41] How trabectedin is affecting all of these cellular properties is not clear. More studies are needed to elucidate mechanisms of action of trabectedin in relation to its clinical effectiveness and identify tumor types that will be most sensitive to inhibition of the pathways by trabectedin.

In summary, trabectedin is an alkylating agent that binds DNA. Many ramifications of this binding activity have been proposed. These include direct and indirect DNA damage, inhibition of transcription factor activity, and changes in down stream cellular behaviors. Further studies need to be conducted to determine which functions of trabectedin have clinical importance.

Metabolism and Pharmacokinetic Profile of Trabectedin

The detailed metabolic studies of trabectedin are limited. Trabectedin is mostly excreted in urine (5%) and feces (55%).[42] The amount of trabectedin that was unchanged in excreted urine and feces was less than 1%, suggesting that most of the trabectedin is converted into other metabolites.[42] There are several sites for metabolic conversion of trabectedin, which is probably one of the reasons there are numerous metabolites.[43] Demethylation and oxidation play a role in trabectedin metabolism.[44] Also trabectedin can be conjugated by both uridine diphosphoglucuronosyl transferase and glutathione-S-transferase.[45]

The cytochrome P450 (CYP) isozyme CYP3A4 appeared to be the major CYP involved in trabectedin breakdown. CYP2C9, CYP2D6, CYP2C19, and CYP2E1 played minor roles in the metabolism of

this compound.[45,46] The metabolism of trabectedin is very complex and only recently the structures of its metabolites have been identified.[43,44] Understanding the metabolism of trabectedin and the toxicity of its metabolites is important for assessing the safety of trabectedin in cancer patients. Mice lacking the drug transporters ABCB1a, ABCC2, and CYP3A have decreased hepatotaxicity compared to wild type mice (or even CYP3A deficient mice),[47] suggesting that the generation and clearance of these metabolites are important in toxicity. Understanding the metabolism and toxicity of the metabolites will be very critical in managing trabectedin therapy in patients.

Since CYP3A4 is the major metabolizing CYP isozyme, coadministration of drugs that are known inhibitors or inducers of CYP3A4 should be avoided.[48] On the other hand, although coadministration with CYP inducers may alter its pharmacokinetics, it appears that the CYP inducers dexamethasone and rifampicin had no effect which allows their coadministration with trabectedin. In animal studies, pre-administration of dexamethasone reduced the level of trabectedin in the liver but not the blood.[49] Pretreatment of patients with dexamethasone or rifampicin is important as both improve the tolerability of trabectedin as explained below under safety and tolerability of trabectedin.

Numerous pharmacokinetic studies have been performed for trabectedin and are reviewed elsewhere.[50–52] Based on available data from several phase I trials, trabectedin demonstrated a linear and dose-proportional pharmacokinetic properties over a wide tested dose ranging from 0.05 to 1.8 mg/m^2 given over 1, 3, or 24 hours infusion.[53,54] Furthermore, administration of trabectedin every three weeks did not cause any accumulation in plasma. Trabectedin is extensively bound to plasma proteins with large volume of distribution at a steady state (Vss) ranging from 570 to 5300 L, corresponding to doses of 0.05 to 1.5 mg/m^2.[53] The mean area under the curve (AUC) was 45.5 ± 20.7 ng.h/mL and the maximum plasma concentration (Cmax) of trabectedin was 1.34 ng/mL in patients with STS who received 1.5 mg/m^2 trabectedin over a 24-h intravenous (I.V.) infusion.[54,55] Trabectedin has a long plasma half life up to 180 hours.[55] The mean body clearance CL was 63.2 ± 30.8 L/h/m^2.[55] The clearance of trabectedin is affected in patients with hepatic dysfunctions and that leads to increased plasma concentration of trabectedin and increased risk of toxicity. Dose adjustment is necessary in these patients to decrease the risk of hepatotoxicity.[54] Several studies showed that patients with mild to moderate renal impairment can be safely treated with trabectedin. However, patients with severe renal impairment with creatinine clearance (CrCl) <30 mL/min should not be treated with trabectedin because of insufficient data about its effect in this specific population, therefore CrCl should be monitored on a regular basis in order to prevent any complications.[53,54]

A population pharmacokinetic analysis showed that the plasma clearance CL and volume of distribution Vd of trabectedin are not affected by gender or age.[54] Additionally Administration of other antineoplastic medications such as pegylated liposomal doxorubicin (PLD), doxorubicin, cisplatin and gemcitabine with trabectedin did not appear to affect the pharmacokinetic properties of trabectedin. Moreover, there were no significant interactions between these agents and trabectedin.[56–59]

Safety and Tolerability of Trabectedin

The toxicity profile and tolerability of trabectedin have been reviewed elsewhere.[50–52,60] Studies conclude that the dose limiting toxicity (DLT) for trabectedin occurred at 1200–1800 mcg/m^2.[53,61] Like other chemotherapeutic drugs including alkylating agents, bone marrow toxicity is a common side effect. The most common bone marrow toxicities observed were grade 3 or 4 neutropenia and thrombocytopenia.[50,51,53,62,63] Hepatic toxicity is detected as grade 3 or 4 alanine transaminase (ALT) or aspartate transaminase (ASP) elevation which may occur in 26%–59%.[50,51,64] Both bone marrow and liver toxicities are generally rapidly reversible, which allows treatment of patients with trabectedin for considerable time periods.[65] Premedication of patients with dexamethasone reduces the incidence of severe hepatic toxicities and myelosuppression and improves tolerability of trabectedin. For example, in STS patients, dexamethasone reduced their levels of transaminases from 70% to 3%, neutropenia from 39% to 10%, and thrombocytopenia from 35% to 0%.[66] Furthermore, prophylactic colony stimulating factors (CSFs) were shown to reduce neutropenia in STS patients evaluated for a combination of trabectedin and doxorubicin.[67] A phase II trial is currently

underway evaluating effect of the CSFs filgrastim, or pegfilgrastim on trabectedin-caused toxicities in patients with OVCA, peritoneal cancers, or fallopian tube cancers treated with a combination of trabectedin and docetaxel.[68]

In addition, other common toxicities include asthenia, fatigue, nausea, and vomiting which are similar to the adverse events associated with the use of other antineoplastic agents. In order to minimize these side effects, prophylactic pre-treatment with 20 mg dexamethasone intravenously 30 minutes before each trabectedin infusion is prescribed for patients receiving trabectedin. This is because dexamethasone works as an antiemetic agent and it reduces hepatotoxicity and mylosuppression.[69] When trabectedin is used in combination with cisplatin or doxorubicin neutropenia is still the cause of DLT.[58,70] Combination with doxorubicin additionally causes cardiac toxicities, so this is important to monitor in these patients.

Trabectedin in Clinical Studies

The efficacy of intravenous trabectedin was evaluated in OVCA and STS patients either as a single agent or in combination with other chemotherapeutic agents. Clinical evaluation of therapy with trabectedin by these studies was based on assessment of patient outcomes according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria, or World Health Organization (WHO) criteria. On the other hand, for STS other acceptable clinical end points have resulted that do not necessarily reflect RECIST tumor shrinkage, but instead reflect disease stabilization, as measured by progression-free rate or progression free survival.[33,71] Clinical trials since 2005 are summarized in this section.

Single Agent Trabectedin in OVCA

In OVCA, patients are classified according to their progression-free interval (PFI, also referred to as platinum-free interval) which refers to the time before they relapse after completion of initial platinum-based therapy. Patients with PFI $\geq$ 12 months are considered to have platinum-sensitive OVCA, those with PFI $<$ 6 months are considered to have platinum-resistant OVCA, and those with intermediate PFI ie, 6–12 months are considered to have partial platinum-sensitive OVCA.[72] For platinum-sensitive patients (PFI $\geq$ 6) platinum-based mono- or combination therapy (carboplatin with paclitaxel, gemcitabine or PLD) is the standard. The readers are referred to recent reviews for more information on the response rates to these chemotherapies.[73,74]

Three phase II trials (Sessa et al 2005,[62] Krasner et al 2007[75] and del Campo et al 2009)[64] evaluated the efficacy of trabectedin in platinum-sensitive patients (PFI $\geq$ 6 months) and platinum-resistant patients (PFI $<$ 6 months) with advanced ovarian cancer (Table 1).[62,64,75] The readers are referred to an elaborate recent review of the results of these three trials by Cassier and coworkers[72] as we will present only a brief summary here of these results. The phase II study by Sessa and coworkers[62] compared the efficacy of trabectedin in 59 patients with recurrent OVCA of which 51 were evaluable according to RECIST: 29 (of which 23 were evaluable) platinum-sensitive patients versus 30 (of which 28 were evaluable) platinum-resistant patients. Trabectedin was initially administered at 1.65 mg/m^2 over 3 hours (h) every 3 weeks (q3wk) which was decreased to 1.5 and then to 1.3 mg/m^2 because of hepatic toxicity. Platinum-sensitive patients were

Table 1. Efficacy of single-agent trabectedin in patients with OVCA.

Study	Treatment regimen	# of patients	Median TTP (mo)	Median OS (mo)	ORR%	Median PFS (mo)
Sessa 2005[62]	1.3 mg/m^2 q3wk	59 (30S, 29R*)	7.9 S*	–	43% S*	–
Krasner 2007[75]	0.58 mg/m^2 qwk for 3 wks of 4	147 (66S, 81R*)	5.2 S* 2.0 R*	– 10.7 R*	29% S* 6.3% R*	5.1 S* 2.0 R*
Del Campo 2009[64]	1.5 mg/m^2 q3wk	54 (49S, 5R*)	6.2	7.1	38.9%	–
	1.3 mg/m^2 q3wk	53 (51S, 2R*)	6.8	6.4	35.8%	–

Notes: *S = platinum-sensitive; R = platinum-resistant.

responsive to trabectedin where overall response rate (ORR) was 43% and the median time to progression (TTP) was 7.9 months, one patient achieved complete response and 9 patients achieved partial response.[62] As for the resistant patients 64% of them progressed with 22% occurring after the first cycle of treatment.

Krasner et al[75] investigated a relatively lower dose (0.58 mg/m^2) with 141 OVCA patients (62 sensitive, 79 resistant) who were evaluable for efficacy according to RECIST. Trabectedin was given once a week at 0.58 mg/m^2 over 3 h intravenous infusion repeated for three weeks followed by one week rest.[75] The ORR of platinum-sensitive and platinum-resistant patients were 29% and 6.3% respectively. In platinum-sensitive patients, the median progression-free survival (PFS) was 5.1 months, and in platinum-resistant patients it was 2 months. Overall, these studies showed that trabectedin is effective as single agent in patients with platinum-sensitive refractory ovarian cancer, while the response was low in platinum-resistant patients.

The del Campo study[64] was designed to evaluate the optimal dose of trabectedin as a single agent in patients with platinum-sensitive relapsed advanced OVCA. This study compared trabectedin at 1.5 mg/m^2 every 24 h (q24h) (n = 54) versus 1.3 mg/m^2 q3h (n = 53), both regimen given q3wk. A total of 107 patients were randomized between these two schedule regimens. In the primary intention to treat (ITT) analysis the ORR was 38.9% in patients receiving the 24-hr infusion and 35.8% in the 3-hr infusion with median TTP of 6.2 months vs. 6.8 months in 24 hr and 3 hr schedules, respectively. Toxicities were comparable with hepatic toxicity and neutropenia in both groups. This indicated that both schedules have similar efficacy and tolerability in patients with recurrent ovarian cancer.[64]

Adverse events were generally comparable across studies using similar dosages of trabectedin, where incidences of neutropenia and thrombocytopenia were generally of short duration and associated with rapid recovery. The Krasner and coworkers study[75] exhibited a dose-related reduction in adverse events such as neutropenia and thrombocytopenia, whereas incidences of anemia were similar to other studies.

Trabectedin in Combination Chemotherapy in OVCA

Trabectedin has been evaluated in combination with pegylated liposomal doxorubicin (PLD, Doxil in USA, Caelyx in Europe) in patients with relapsed OVCA. The maximum tolerated dose (MTD) of this combination was determined in a phase I trial to be 1.1 mg/m² trabectedin and 30 mg/m² PLD (the study had 16 STS and 4 OVCA cases out of 36 patients). The ORR was 16.7% with one complete response (CR) and 5 partial response (PR).[56]

The efficacy of this regimen was further studied in a randomized phase III study (referred to as OVA-301) where PLD was infused over 90 min followed by 3 h trabectedin q3wk (n = 337) and this was compared to PLD 50 mg/m^2 over 90 min q4wk (n = 335) in patients with recurrent ovarian cancer.[59] The study showed that for platinum-sensitive patients there was a six week increase in median PFS by trabectedin/PLD combination over PLD alone (9.2 months vs. 7.5 months), and overall the ORR was 35% vs. 23%. An updated median overall survival (OS) (the final OS is not yet available) after an additional year of follow-up for all the evaluated population was 22.4 months versus 19.5 months.[76] Nevertheless, the trabectedin/PLD combination treatment did not provide additional benefits for the platinum-resistant subgroup. Both treatment arms also reported patients achieving complete response to treatment (trabectedin/PLD combination 7% and PLD alone 4%).

Although the trabectedin/PLD combination increased PFS to 7.3 months from 5.8 months with PLD monotherapy, it increased adverse effects including hematologic, cardiac and hepatic toxicities. In addition, this combination has not been compared to the preferred platinum-based mono- or combination therapies to determine its clinical benefit for these patients and weigh this against the toxicity of this combination. These are the reasons why this combination has not been approved in the USA for therapy of ovarian cancer patients. On the other hand, in contrast to taxanes and platinum-based chemotherapeutic agents, the trabectedin/PLD combination had lower incidence of neuropathey and alopecia. This indicates that this combination may be useful in women with platinum hypersensitivity or peripheral neuropathy.

Further follow-up of a subset of patients of this study (n = 214) with partially platinum-sensitive relapse (6–12 months PFI)[76] reported a PFS of 7.4 months versus 5.5 months for combination versus PLD alone therapy, and median OS was 23 months versus 17.1 months.[76] Indeed this higher clinical benefit to this subgroup of OVCA patients was also reported with single-agent therapy with trabectedin.[77] Subsequent third-line therapies on 77% of the patients in OVA-301 (77% PLD versus 76% trabectedin/PLD) showed a 2.5 months delay in time for subsequent therapy in trabectedin/PLD versus PLD arm.[78] These differences were larger in the PFI 6–12 months subset as evident by the delayed subsequent platinum therapy by a median of 4 months in addition to enhanced survival.[78] This was possibly due to extension of the PFI coupled with longer survival after the start of subsequent platinum-based therapy. The same group is currently preparing to test this hypotheses through planning a large, randomized clinical trial.[78]

In addition to combination with PLD, a combination of trabectedin and cisplatin was evaluated in a phase I trial. Trabectedin was administered as a 3 h IV infusion, starting at 300 μg/m^2 (increased by 100 μg/m^2 when tolerated), in combination with 40 mg/m^2 cisplatin, both given on day 1 and 8 q3wk.[58] This study demonstrated that the recommended dose of trabectedin to be combined with cisplatin was 500 μg/m^2 on chemotherapy-experienced patients, and 600 μg/m^2 in naive patients. This study showed that there were no added benefits from using this combination in comparison to trabectedin alone. Overall this regimen was not well tolerated with low efficacy due to neutropenia which caused treatment cycle delays.[58] An additional combination that is currently being evaluated is that of combining trabectedin with docetaxel which seems to be more beneficial than single agent taxane therapy in recurrent ovarian and peritoneal cancers.[79]

Trabectedin combination treatment was associated with an increase in many of the hematological and non-hematological adverse events over PLD single treatment, particularly severe neutropenia (63% vs. 22%) and thrombocytopenia (18% vs. 2%); whereas ALT elevations (31% vs. 0.3%) were reported to be transient and noncumulative. Incidences of severe febrile neutropenia were also more common in the combination group (7% vs. 2%). On the other hand, when PLD was combined with trabectedin, common adverse events associated with PLD therapy such as hand-foot syndrome, mucosal inflammation and stomatitis were less. Combination with PLD resulted in some cases (six) of nonfatal congestive heart failure.

The above studies demonstrated that the combination of trabectedin with PLD is beneficial for OVCA patients who are either sensitive or partially sensitive to platinum therapy. However, platinum-resistant patients will not benefit from trabectedin alone or in combination. Nevertheless, there is evidence from preclinical and retrospective clinical data demonstrating that patients with resistance or partial resistance to platinum will respond to it after therapy with a non-platinum agent.[80] Thus delaying re-introduction of platinum and treating with a non-platinum agent in between platinum treatments may be beneficial to resistant or partially resistant patient.

Single-Agent Trabectedin in STS

Trabectedin demonstrated high efficacy as a second-line therapy for patients with metastatic STS who are resistant to chemotherapy with doxorubicin and ifosfamide. In particular, it has been effective against liposarcomas, leiomysarcomas and synovial sarcomas. The standard administration schedule for trabectedin has been 1.5 mg/m^2 over 24 h every three weeks (q3wk).[52,65] Evaluation of the efficacy of the standard dose was done in Phase II trials in either chemotherapy-naive patients or pre-treated patients with advanced soft tissue sarcoma (Table 2).[55,81] The majority of patients in these studies received dexamethasone IV before trabectedin infusion as a prophylactic treatment to reduce liver toxicity. The median TTP reported in these studies was 1.7–3.5 months with median duration of response ranging from 9.2 to 12.1 months. These studies indicated that trabectedin is an effective and valuable treatment for patients with recurrent STS as a second line therapy after failure of previous conventional chemotherapy[81] or even as a first line therapy.[55] For the multicenter phase II study with chemotherapy-naive patients the dose of trabectedin was reduced to 1.2 mg/m^2 because of hepatic toxicity.[55] The OSR was 72% with median survival of 12.1 months. Moreover, the objective response

Table 2. Efficacy of single-agent trabectedin in patients with advanced recurrent STS.

Study	Treatment regimen	# of patients	Median TTP (mo)	Median OS (mo)	ORR%	Median PFS (mo)
Le Cesne 2005[81]	1.5 mg/m^2 q3wk	104	3.5	9.2	8%	3.4
Garcia-Carbonero 2005[55]	1.5 mg/m^2 q3wk	36	1.7	12.1	17.1%	1.6
Huygh 2006[87]	0.9–1.5 mg/m^2 q3wk	89	2.0	8.2	6.7%	2.0
Roylance 2007[82]	0.9–1.5 mg/m^2 q3wk	22	3.9	9.9	–	4.5
Demetri 2009[65]	1.5 mg/m^2 over 24 h q3wk	136	4.2	13.9	5.6%	3.3
	0.58 mg/m^2 over 3 h qwk for 3 wks q4wk	134	2.5	11.8	1.6%	2.3

(OR) was 17% and median duration of response was 16.5 months. This study demonstrated the efficacy of trabectedin in chemotherapy naive patient with advanced STS with manageable safety profile of mainly hepatotoxicity and neutropenia.[55]

The efficacy of the use of the regimen of 1.5 mg/m^2 over 24 h q3wk was further confirmed by a phase II randomized trial, where two infusion schedules were compared for trabectedin;[65] infusion of 1.5 mg/m^2 over 24 h, q3wk versus three 3 h infusions of 0.58 mg/m^2 every week (qwk) for three weeks of a four-week cycle (3-h qwk). It was found that the q3wk schedule was more effective than the qwk in prolonging the median PFS (3.3 months vs. 2.3 months) whereas OS was not statistically significant between the two arms[65] as summarized in Table 2.

The efficacy of intravenous trabectedin in STS patients for recent studies is summarized in Table 2. Two studies on patients with advanced STS showed comparable results: the efficacy of Roylance 2007 trial[82] was comparable to the phase II trial by Le Cesne 2005 as summarized in Table 2.[81] Le Cesne 2005 also reported a 12-month overall survival of 44 patients (42%) while Roylance reported 17.6% of patients had stable disease (SD) >6 months. Six patients underwent radical surgical resection after trabectedin and became disease-free.

In Grosso 2007 trial,[33] a study on 51 patients, the efficacy of trabectedin was significantly higher than other studies where ORR was 51%, median PFS was 14 months and 88% had SD > 6 months. The reason for this, was that the patients were mainly myxoid liposarcoma patients who represent a subset STS patients with high sensitivity to trabectedin. This sensitivity was attributed to trabectedin's inhibition of activation of the overexpressed FUS-CHOP oncogene in myxoid liposarcoma as explained above under mechanism of action.[37]

Trabectedin in Combination Chemotherapy in STS

Trabectedin in combination with other chemotherapeutic agents such as doxorubicin, paclitaxel, and gemcitabine were evaluated in phase I studies for safety. Two studies evaluated trabectedin in combination with doxorubicin which is one of the first line chemotherapeutic agents used in STS.[67,70]

In an effort to minimize the risk of myelotoxicity while maintaining full single-agent dose of trabectedin in combination with doxorubicin, Blay et al 2008 pretreated patients with a prophylactic granulocyte colony-stimulating factor (G-CSF). With the maximum tolerated dose (MTD) of 1.1 mg/m^2 trabectedin and 60 mg/m^2 doxorubicin, the reported grades 3 and 4 toxicities were: 71% neutropenia, 37% thrombocytopenia, and 46% increased ALT.[67] Trabectedin at 0.9 mg/m^2 combination with doxorubicin was associated with similar hematological toxicities. The other phase I study by Sessa and coworkers[70] employed a lower dose of trabectedin (MTD 0.8 mg/m^2) combined with the same dose of doxorubicin. The common toxicities were increases in AST/ALT and neutropenia.[70]

After a median of six cycles in both studies, the percentages of patients achieving partial response were close; 12% in the Blay and coworkers study[67] and 18% in the study by Sessa and coworkers[70] and SD for STS was 80% (37% >6 months) and 46% in the respective studies. More importantly, the median PFS of 9.2 months[67] and 12.5 months[70]

were significantly superior to trabectedin single treatment shown in Table 2. One patient with malignant schwannoma achieved complete response after study withdrawal.[70]

Besides the combination with doxorubicin, trabectedin was combined with paclitaxel or gemcitabine and these combinations were evaluated in solid tumors for safety in phase I trials. For the study conducted to examine the safety of trabectedin in combination with paclitaxel,[83] a total of 27 patients were enrolled and received 80–120 mg/m^2 of paclitaxel 1 h IV infusion on day one and 0.525–0.775 mg/m^2 trabectedin 3 h infusions every 2 weeks. This study determined the MTD to be 0.650 mg/m^2 of trabectedin and 120 mg/m^2 of paclitaxel administered every two weeks. Overall, one STS patient achieved a complete response and 10 patients had stable disease (6 of them had STS). This study demonstrated that trabectedin in combination with paclitaxel is well tolerated at the determined MTD.[83]

In another study, a combination of 0.3 to 0.4 mg/m^2 trabectedin and 900 to 1000 mg/m^2 of gemcitabine were administered for three weeks q4wk.[57] Hepatic toxicity caused excessive changes to the dose schedules which led to early termination of the study. There were no complete or partial responses reported in this study, but 2 patients had stable disease after 2 treatment cycles. It was not possible to determine a DLT for this combination in this study. The most common drug related issues that required cycle delay or dose reduction were elevated AST, ALT, neutropenia and thrombocytopenia. This study showed that there were no drug interactions between trabectedin and gemcitabine; however, further evaluation is needed with alternative dosing schedules.

These studies demonstrated that it is safe to administer trabectedin in combination with other chemotherapeutic agents; although it seems that the dose of trabectedin needs to be reduced and dosing schedules may need adjustment such as the case of combination with gemcitabine.

Place in therapy

In October 2009 and based on the results of Monk and coworkers 2010,[59] the European Union Commission approved trabectedin combined with PLD for the treatment of patients with relapsed, platinum-sensitive OVCA. The recommended dosage is a 3-wk cycle of administring 30 mg/m^2 PLD followed by 1.1 mg/m^2 trabectedin over 3 hours with dose modification if necessary.[84] The recent studies demonstrating the utility for this combination for the partially-sensitive OVCA patients may extend approval for this combination to this subgroup of OVCA patients. This therapeutic combination is not yet approved in the USA for therapy of OVCA. As for STS, trabectedin is approved as a single agent for second line therapy of recurrent or metastatic STS, in the USA and Europe. The recommended dosage is 1.5 mg/m^2 administered over 24 h q3wk with dose modification if necessary.[84] In particular trabectedin has high activity in myxoid liposarcoma patients and is commonly used for liposarcoma and leiomyosarcoma patients.[11–13,50]

Conclusions

Prediction of cancer sensitivity or resistance to trabectedin can be attained through biomolecular analysis of genes involved in DNA repair such as BRCA1/2 and XPG or those involved in trabectedin metabolism such as CYPs as this will enhance personalized medical treatments. Because of the risk of drug-drug interactions, combination of trabectedin with inducers or inhibitors of CYP3A4 should be avoided unless new dosing schemes are developed to take into account these interactions. On the other hand, pretreatment with the CYP inducer dexamethasone has shown great potential in improving the tolerability of trabectedin. Currently CSFs are being evaluated for reducing myelosuppression caused by trabectedin.

Studies indicate that trabectedin is an effective and valuable treatment for patients with recurrent STS as a second line therapy after failure of previous conventional chemotherapy. In addition, phase I trials indicated that combination therapy, especially with doxorubicin[67,70] may be more beneficial for STS than trabectedin alone. Nevertheless, phase II clinical trials are needed to show evidence for the efficacy of this combination in comparison to other regimens. A recently reported STS case treated with trabectedin[85] suggests that tumor density based on computed tomography (CT) may be a better response evaluation criteria than tumor shrinkage as determined in RECIST.[85] A similar proposal was previously made for metastatic gastrointestinal stromal cancers using therapeutic agents other than trabectedin.[86] Recently

disease stabilization was added as an acceptable end point for evaluation of STS patients' response in addition to the WHO criteria and RECIST criteria.[33,71] Further evaluation of adding tumor density as an acceptable criteria is warranted.

Trabectedin/PLD combination is currently approved in Europe, but not the USA, for treatment of platinum-sensitive OVCA patients. In addition, recent studies are demonstrating clinical benefits for the partially-sensitive subgroup. On the other hand, no benefit has been demonstrated for the platinum-resistant OVCA patients. Demonstrating the benefit of using trabectedin/PLD combination over platinum- or taxane-based therapies is recommended. Furthermore, further work is needed to evaluate the clinical benefits of combining trabectedin with platinum- or taxane-based therapies, which are in progress.[58,79] Future studies may evaluate combination of trabectedin with biological therapies (molecular or targeted therapies) for OVCA or STS.

Trabectedin leads to severe hepatic and bone marrow toxicities and prophylactic treatment is usually prescribed to reduce these side effects. Nevertheless, development of other options for reducing the toxicity of trabectedin could be explored. For example employing nanotechnology approaches such as encapsulating trabectedin in liposomes or biodegradable polymeric nanocarriers has great potential in reducing its toxicity through passive targeting of the cancer or what is referred to as enhanced permeability and retention (EPR) effect.

Disclosures

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List of Abbreviations

OVCA, ovarian cancer; STS, soft tissue sarcoma; NER, nucleotide excision repair; HR, homologous recombination; DSB, double strand breaks; ERCC1, excision repair cross-complementing rodent repair deficiency, complementation group 1; BRCA1/2, breast cancer type 1/2 suseptability protein; XPG, xeroderma pigmentosum group G; E2F, elongation 2 factor; SP-1, specificity protein-1; SRF, serum response factor; NF-Y, nuclear transcription factor Y; TBP, TATA binding protein; VP16, herpes virus transactivator; CTF, CCAAT box-binding transcription factor; MDR1, multidrug resistance gene; MLS, myxoid liposarcoma; CHOP, C/EBP homologous protein 10; C/EBP, CAAT-enhancer binding protein; FUS, fused in sarcoma; TAM, tumor associated macrophages; CCL2, chemokine (C-C motif) ligand 2; IL-6, interleukin-6; JNK, c-jun kinase; CYP, cytochrome P450; AUC, area under the curve; CrCl, creatinine clearance; IV, intravenous; PLD, pegylated liposomal doxorubicin; CSF, colony stimulating factor; DLT, dose limiting toxicity; ALT, alanine transaminase; ASP, aspartate transaminase; RECIST, response evaluation criteria on solid tumors; WHO, world health organization; PFI, progression-free interval or platinum-free interval; ORR, overall response rate; TTP, time to progression; PFS, progression-free survival; ITT, intention to treat; MTD, maximum tolerated dose; PR, partial response; OS, overall survival; OR, objective response; SD, stable disease.

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