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A comprehensive review of the current evidence for trabectedin in advanced myxoid liposarcoma

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ABSTRACT

Myxoid liposarcoma (MLS) is a rare mesenchymal tumor that constitutes 10–20% of all liposarcomas. MLS is a translocation-related sarcoma (TRS) related to the chromosomal translocation t(12:16) (q13:p11), producing the FUS-CHOP oncoprotein that constitutes one of the main targets of trabectedin in MLS patients. It is known to be chemosensitive namely to trabectedin in contrast to other soft tissue sarcomas. The efficacy of this agent in MLS have been demonstrated in different settings including treatment-naïve and pre-treated patients with both locally advanced and metastatic disease. However, the benefits of trabectedin in MLS are shadowed by the limited activity of this drug in other subtypes of sarcomas that are enrolled within the same trials. This prompted us to screen the medical literature for clinical data that evaluates the efficacy and safety of trabectedin in MLS. In this review, we will summarize the available evidence for the applicability of trabectedin in MLS.

Introduction

Myxoid liposarcomas (MLS) constitute almost 10–20% of all liposarcomas and 5% of all soft tissue sarcomas (STS) [1,2]. Its incidence peaks in the fourth and fifth decade of life with an equal distribution between men and women [1]. At presentation, one third of MLS patients are metastatic mainly to extrapulmonary sites such as the retroperitoneum, axilla and bones [2,3]. MLS is characterized by the chromosomal translocation t(12:16) (q13:p11) present in 95% of patients and producing the FUS-CHOP oncoprotein [3]. Other MLS associated genetic aberrations have been less frequently described such as t(12;22) (q13;q12) [4,5], PI3KCA mutations [6], homozygous loss of PTEN, high expression of RET, IGF1R and IGF2 [7,8]. However, the diagnosis of MLS still relies on the pathologic findings of a nodular growth pattern with a mixture of uniform round to oval non-lipogenic cells and small signet ring lipoblasts in a myxoid stroma with a rich capillary network. A gradual progression of MLS to hypercellular or round cell morphology has also been described and reported to determine a poor prognosis [2]. Other predictors of unfavorable outcomes include high grade tumors with more than 5% of round cells, alteration within the TP53 and CDKN2A genes and presence of necrosis on pathology [9]. Nevertheless, MLS is sensitive to conventional chemotherapy in contrast to other STS [10–12].

Trabectedin was initially approved in Europe in 2007 and subsequently in the USA in 2015 in advanced pretreated L-STS tumors (Liposarcomas and Leiomyosarcomas). It is a marine-derived anti-neoplastic agent that has shown encouraging responses in STS and particular efficacy in many retrospective and prospective trials of MLS [13–16]. Because of the low incidence of MLS, patients eligible for clinical trials are pooled with other mediocre STS which may limit the identification of sarcoma subtypes in which treatment would have been beneficial. As such, there is no solid data that favors the use of trabectedin in MLS [13,17]. However, patients are more prone to receive trabectedin with the benefits observed in real-life studies [18]. In order to better understand the rationale, efficacy and safety of trabectedin in MLS, we will provide a comprehensive review on this topic across the different stages of the disease.

Rationale for trabectedin in MLS

Chromosomal translocations constitute the most frequent molecular alterations in sarcomas and occur in around one fifth of these patients [19]. MLS is a translocation-related sarcoma (TRS) related to the chromosomal translocation t(12:16) (q13:p11), producing the FUS-CHOP oncoprotein which binds to DNA promoters and deregulates the expression of downstream proteins [3,20].

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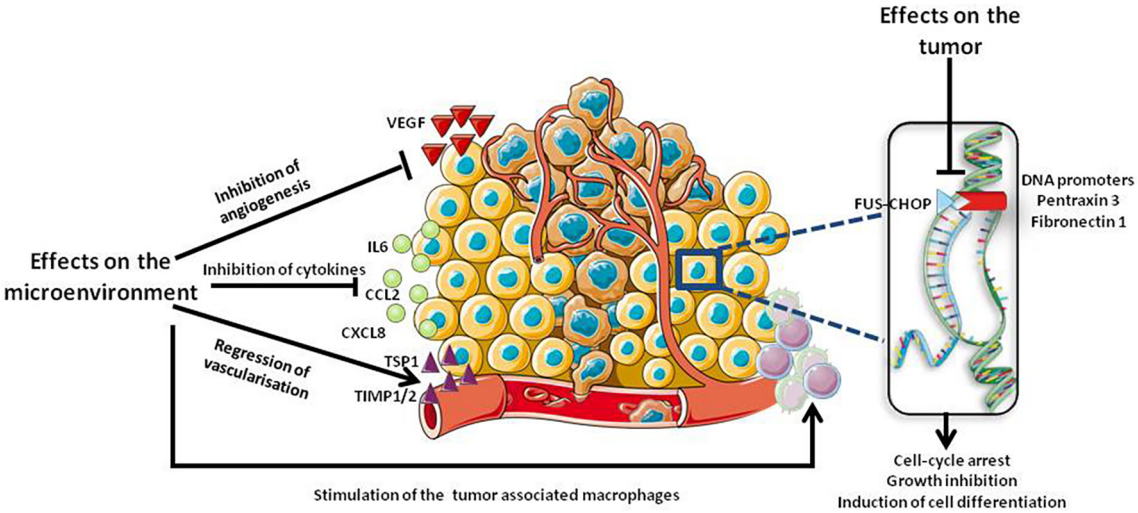

Fig. 1. Overview of the trabectedin activity on both cancer cells and the tumor microenvironment.

Trabectedin has shown a pleiotropic spectrum of antitumor activities (Fig. 1) in some forms of TRS mainly MLS as well as synovial sarcoma (SS) and alveolar soft part sarcoma [21,22]. It has a complex mechanism of action affecting key cell biology processes in tumor cells as well as in the tumor microenvironment resulting in cytotoxic and antiproliferative effects, inhibition of gene transcription, as well as immunologic and antiangiogenic actions. These effects are mediated by the inhibition of active transcription and blockade of DNA repair and generation of DNA breaks [23].

The inhibition of active transcription results from the binding of trabectedin to the DNA minor groove and its effect on the promoters that bind to the major groove [24]. Trabectedin directly blocks RNA polymerase II during elongation which induces its rapid and massive degradation by the proteasome pathway [25,26]. The degradation of RNA polymerase II though initial direct mechanisms which subsequently modulate the production of cytokines and chemokines by tumor and tumor-associated macrophages. Thus, trabectedin exerts an immunologic effect by targeting the inflammatory mediators in the tumor microenvironment and reducing the expression of several growth factors and cytokines (CCL2, CXCL8, IL6, VEGF) as well as other matrix-binded proteins such as pentraxin 3 (PTX 3). A xenograft mouse model of MLS human cells demonstrated that trabectedin decreased CD68+ macrophages and CD31+ tumor vessels within the tumor microenvironment [27]. Trabectedin also induces structural changes of the DNA that might displace the transcription factors from their target gene promoters [28]. In MLS, trabectedin interferes with the binding of FUS-CHOP to the DNA promoters (Pentraxin 3 or Fibronectin 1), stimulates tumor differentiation and reappearance of mature lipoblasts by reducing the oncoproteins FUS-CHOP types I and II [29,30]. For instance, MLS patients with pathological complete remission (pCR) to neoadjuvant trabectedin were devoid of tumor tissue and no FUS-CHOP transcripts *(absence of transcript detection by polymerase chain reaction (PCR) is one of the main criteria to confirm pathological CR)* were detected in the post-surgical specimens [31].

Trabectedin blocks DNA repair and generate DNA breaks as the DNA adducts formed by trabectedin hamper the nucleotide excision repair (NER) machinery and thereby inhibits the repair of specific NER substrates [32]. This finally gives rise to the generation of double strand DNA breaks that could be repaired by homologous recombination, otherwise monoadducts mimic interstrand crosslink and hamper transcription and replication [33]. The degradation of RNA polymerase II is dependent on the presence of a proficient transcription-coupled NER system [25]. Thus, the combination of trabectedin with PARP inhibitor in the treatment of sarcomas seems rational and promising [34,35].

Recent evidence has shown that trabectedin targets key processes in the tumor microenvironment. It has been shown that trabectedin exerts antiangiogenic actions by regressing the capillary networks within the tumor through the upregulation of the matrix metalloproteinases TIMP-1 and TIMP-2 inhibitors as well as the tumor cell expression of the endogenous inhibitor thrombospondin-1 (TSP-1) [36]. Moreover, trabectedin causes monocyte depletion including tumor-associated macrophages to locally activate the immune system which constitute the backdrop for the combination of trabectedin and immune checkpoint inhibitors [23,37].

Trabectedin in pre-treated metastatic and unresectable MLS patients

Table 1 reports on the efficacy outcomes of MLS subgroups treated with trabectedin in previously treated patients. The initial trials of trabectedin were restricted to small phase II trials enrolling pretreated STS patients after failure of conventional chemotherapy. These studies reported an overall response rate (ORR) of 8–14% and median overall survival (OS) of 7.8–12.8 months [38–40]. Further trials of trabectedin in STS evaluated the administration regimens (1.5 mg/m^2 every 3 weeks vs 0.58 mg/m^2 weekly) and demonstrated survival benefit (OS 13.9 vs 11.8 months) with a three-week schedule [15]. Continuous trabectedin until progression was approved in Europe based on these results for pretreated STS patients after failure of anthracyclines. Further data from a phase II trial randomizing patients to continuing trabectedin until progression or interruption after 6 cycles did not show a survival benefit favoring any of the two arms [41]. The initial results showed difference in PFS between the two groups but long term results demonstrated the absence of difference in OS thus suggesting that interruption of trabectedin with rechallenge upon progression is an acceptable approach [42].

After the positive outcomes of trabectedin in few MLS cases [40,43], Grosso et al. reported the first solid data on the sensitivity of MPS to trabectedin [13]. This retrospective series of 51 patients showed ORR of 51%, median progression free survival (PFS) of 14 months and 6-month PFS of 88%. More importantly, radiological responses were sometimes identified due to density modifications (CHOI criteria) before size changes (RECIST criteria) [44]. The long term follow-up of 32 patients from this study has demonstrated a median PFS of 17 months that reached 28.1 months in 10 patients with CR following surgical removal of residual disease [13]. Another retrospective series of 62 MLS patients treated with trabectedin showed similar results with ORR of 58%, disease control rate (DCR) of 87% and median PFS of 14 months. It is noteworthy that non-progressive patients were able to discontinue treatment safely as rechallenging with trabectedin at progression was successful with secondary resistance occurring after 48 months [45].

Table 1
Efficacy outcomes of MLS subgroups treated with trabectedin in previously treated patients.

Author	Study population	N	Study design	Comparative arms	Dose of trabectedin	Number of MPLS patients	ORR (%)	Median PFS (mo)	Median OS (mo)	Additional information
Garcia-Carbonero et al. [43]	Pretreated STS	36	Prospective phase 2	Single arm trabectedin	24-hr at 1.5 mg/m^2 every 21 days	NR	NR	NR	NR	In all patients, 3 responders among which 2 had MLS: 1CR and 1 PR
Grosso et al. [44]	Pretreated MLS	51	Retrospective	Single arm trabectedin	3-hr or 24-hr at 1.1–1.5 mg/m^2 every 21 days	51	51	14	NR	2 patients had CR
Sanfilippo et al. [45]	Pretreated MLS	62	Retrospective	Single arm trabectedin	Not available	62	58	14	NR	In patients with rechallenge, time to secondary resistance is 48 months
Le Cesne et al. [22]	Pretreated TRS	81	Retrospective	Single arm trabectedin	3-hr or 24-hr at 1.1–1.5 mg/m^2 every 21 days	27	15	9	18.3	In all patients, ORR of 10% and median PFS and OS of 4.1 and 17.4 months
Kawai et al. [46]	Pretreated TRS	76	Prospective randomized phase 2	Trabectedin (A) vs BSC (B)	24-hr at 1.2 mg/m^2 every 21 days	24	12.5	7.3 (A) vs 0.9 (B)	NR	In all the patients, median PFS of 5.6 (A) and 0.9 (B) months/ 3 PRs in MLS
Demetri et al. [14]	Pretreated L-STS	518	Prospective randomized phase 3	Trabectedin (A) vs Dacarbazine(B)	24-hr at 1.5 mg/m^2 every 21 days	58	NR	5.6 (A) vs 1.5 (B)	NR	In all the patients, median PFS 4.2 (A) vs 1.8 (B) months

MLS: myxoid liposarcoma; N: number of patients; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; STS: soft tissue sarcoma; TRS: translocation; BSC: best supportive care; L-STS: Liposarcoma and leiomyosarcoma.

Retrospective data from 81 patients with TRS who received trabectedin in the second-line setting in 8 multicentric phase II trials showed an ORR of 10% and median PFS of 4.1 months, 6-month PFS of 40% and median OS of 17.5 months. MLS patients had better outcomes with a median PFS of 9 months, 6 month-PFS of 64% and median OS of 18.3 months [22].

A phase II study of TRS patients demonstrated PFS benefit in favor of trabectedin over best supportive care (5.6 versus 0.9 months) after multiple lines of therapy. This benefit was more prominent in the subgroup of patients with MLS (7.3 versus 0.9 months) (HR = 0.03 (< 0.01–0.22) [46]. In the best supportive care subgroup, the strategy of crossing over to trabectedin was successful and well tolerated with a median PFS of 7.3 vs. 0.9 months in the initial analysis [47]. A confirmatory phase III trial comparing trabectedin and dacarbazine in 518 previously treated patients with liposarcomas and leiomyosarcomas (LMS) showed significant PFS benefit (4.2 vs 1.7 months) (HR = 0.55(0.44–0.70)) in the overall population among which the MLS subgroup benefited the most (5.6 vs 1.5 months) (HR = 0.41(0.17–0.98)). Unfortunately, these results did not translate into an OS benefit in the overall population (12.4 vs. 12.9 months) [14].

Trabectedin in the first-line treatment of metastatic and unresectable MLS

Table 2 reports on the efficacy outcomes of MLS subgroups treated with trabectedin in treatment-naïve patients. With the encouraging signs of trabectedin activity in previously treated STS, several trials have assessed its efficacy in the first-line treatment of metastatic or unresectable STS. One initial phase II trial demonstrated promising activity with an ORR of 17.1% (three out of the six responding patients had MLS) and one-year PFS and OS rates of 21% and 72% respectively. These 3 MLS patients had respectively a PFS and an OS ranging between 17 and 25 months and 21–44 months [40]. Moreover, a major international phase III trial including patients with advanced/metastatic TRS among which one third of whom having a MLS has attempted to evaluate the role of first-line trabectedin in comparison to doxorubicin-based chemotherapy. Unfortunately, this study was terminated in its first stage due to an increased attrition rate (27.3%) and data censoring (67%), mainly related to the surgical removal of remnant tumors which was higher in the trabectedin group (23.5 vs 16.2%) and the addition of a new anticancer therapy before disease progression, which occurred more commonly in the standard chemotherapy subgroup (17.6 vs 24.3%). The survival rates did not differ significantly between the two arms but the survival curves diverged beyond 20 months in favor of trabectedin which reflects the prolonged response encountered in a proportion of patients treated with this drug. Among 121 randomized patients, only 88 patients had confirmed TRS on central review and only 26 patients had confirmed PFS. No significant difference in PFS or OS was detected but as expected, higher toxicity including severe neutropenia, alopecia and mucositis were reported with standard chemotherapy. The MLS subtype was shown to be one of the most favorable prognostic factors in this report [48]. Another phase II trial, the TRUSTS study, enrolling 133 STS patients randomized to doxorubicin, 3-hour trabectedin infusion and 24-hour trabectedin infusion. This study failed to demonstrate any PFS improvement with either of the trabectedin regimens against the doxorubicin with median PFS of 2.8, 3.1 and 5.5 months for the 3-hour trabectedin infusion, 24-hour trabectedin infusion and doxorubicin arms respectively [49].

The limited efficacy of trabectedin monotherapy in the first-line treatment has incited further combination trials. A phase I trial of 41 patients receiving the combination doxorubicin 60 mg/m^2 and trabectedin 1.1 mg/m^2 every three weeks yielded an ORR of 12% (two out of the five responding patients had MLS), DCR of 95% and median PFS of 9.2 months [50]. A phase 2 trial compared the combination regimen to doxorubicin alone in advanced STS but the study was terminated for futility after the interim analyses showed similar efficacy between the two arms (PFS 5.7 vs 5.5 months) but higher rates of toxicity with the

Table 2
Efficacy outcomes of MLS subgroups treated with trabectedin in treatment-naive patients.

Author	Study population	N	Study design	Comparative arms	Dose of trabectedin	Number of MPLS patients	ORR (%)	PFS (mo)	OS (mo)	Additional information
Garcia-Carbonero et al. [40]	TN STS	35	Prospective Phase 2	Single-arm Trabectedin	24-hr infusion at 1.5 mg/m^2 every 21 days	9	33	17–25	21–44	ORR all STS = 17.1% (6 patients) with 3 MLS: 1 CR and 2 PR/ 1-yr PFS and OS = 21% and 72%
Blay et al. [50]	TN STS	41	Prospective Phase 1	Trabectedin + Doxorubicin	24-hr infusion at 0.9–1.3 mg/m^2 every 21 days	NR	NR	NR	NR	ORR of 12% (5 patients) with 2 MLS: 2 partial responses
Blay et al. [48]	TN TRS	133 (88)	Prospective Randomized Phase 3	Trabectedin (A) vs Doxorubicin-based regimen (B)	24-hr infusion at 1.5 mg/m^2 every 21 days	40	NR	NR	NR	According to RECIST: ORR: 5.9% (A) vs 27% (B) (2 out of 3 and 5 out of 10 were MLS in (A) and (B) respectively) According to CHOI: 37.3% (A) vs 45.9% (B)

MLS: myxoid liposarcoma; N: number of patients; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; TN STS: treatment-naive soft tissue sarcoma; TRS: translocation.

Table 3
Efficacy outcomes of MPLS subgroups treated with trabectedin in the neoadjuvant setting.

Author	Study population	N	Study design	Study arms	Dose of trabectedin	Number of MPLS patients	ORR (%)	Median PFS (mo)	Median OS (mo)	Additional information
Gronchi et al. [31]	Neoadjuvant MLS	29	Prospective phase 2	Single-arm Trabectedin	24-hr infusion at 1.5 mg/ m2 every 21 days	29	24	NR	NR	13% pathological CR
Gronchi et al. [17]	Neoadjuvant STS	287	Prospective Randomized phase 3	Histotype-tailored regimen* vs Doxorubicin + Ifosfamide	24-hr infusion at 1.5 mg/ m2 every 21 days	64	NR	NR	NR	HR for DFS in MLS subgroups: 1.03 (0.24–4.39)
Gronchi et al. [52]	Neoadjuvant MLS	14	Prospective phase 2	Single-arm Trabectedin with radiotherapy	24-hr infusion at 1.1–1.5 mg/m^2 every 21 days	13	38	NR	NR	25% pathological CR

MPLS: myxoid liposarcoma; N: number of patients; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; STS: soft tissue sarcoma; TRS: translocation; CR: Complete remission; mo: months.

* Trabectedin was assigned to MPLS subgroup.

combination (mostly asthenia, liver toxicity and thrombocytopenia) [51]. The results of this study were highly questionable because of the variations in the drugs sequencing where trabectedin was administered before doxorubicin in contrast to the phase I trial [50,51].

Trabectedin in the neoadjuvant setting of MLS

The high response rates of trabectedin in MLS have paved the way for neoadjuvant trabectedin in localized tumors. Table 3 reports on the efficacy outcomes of MLS subgroups treated with neoadjuvant trabectedin. In fact, neoadjuvant trabectedin 1.5 mg/m^2 every three weeks exhibited in 29 patients with previously untreated localized operable MLS an ORR of 24% and DCR of 100% [31]. Three out of 23 assessable patients demonstrated a pathological complete response (CR) on the final histological specimen. The pathological specimens showed a maturation of the tumor cells into lipoblasts along with reduction in the cellular and vascular tumor components [31]. More recently, ISG-STS 1001, a randomized controlled phase III trial, has compared conventional chemotherapy (epirubicin 60 mg/m^2 d1-2, ifosfamide 3 g/m^2 d1-3 every three weeks) and histotype-tailored chemotherapy in 287 STS patients. Participants presented the five most frequent STS subtypes: MLS, LMS, synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST), undifferentiated pleomorphic sarcoma (UPS). After a median follow-up of 12.3 months, the standard chemotherapy regimen showed higher projected DFS at 46 months (62 vs 38%) and prolonged survival rates (89 vs 64%). Subgroup analysis of 64 MLS patients showed that only trabectedin patients exhibited equivalent efficacy outcomes with the two regimens [17].In fact, the hazard ratio for disease-free survival (DFS) was 1.03 (0.24–4.39) between the 2 randomized subgroups of MLS patients (36 in the trabectedin arm and 28 in the control arm) [17]. This intriguing finding requires further validation in view of the small sample of MLS patients and the potential differences between the enrolling centers. Furthermore, the addition of radiotherapy (45 Gy) to trabectedin in preoperative locally advanced MLS demonstrated an ORR of 38% and 25% of pathological CR [52].

Real-life experience of trabectedin in STS

Several retrospective series have already reported the real-life experience of trabectedin in STS patients (Table 4). The majority of these studies report on the activity of continuous trabectedin 1.5 mg/m^2 over 24 h every three weeks until progression in previously treated STS. The efficacy of trabectedin reached at best an ORR of 37.8%, DCR of 81.8%, median PFS of 11.6 months and OS of 22.3 months but the variations between the studies were wide. Neutropenia and liver toxicity constituted the most common grade 3/4 side effects with treatment-related discontinuation rates due to toxicity varying reaching 18%. Unfortunately, the performance of MLS patients was rarely reported as a single entity and was probably pooled within the liposarcoma subtypes (Table 4).

One important real-life study reporting on the efficacy of trabectedin in 181 pretreated STS patients within the French compassionate programs showed unexpected results. First, the MLS patients had better OS (33.4 vs. 13.9 months) and PFS (10.5 vs. 2.8 months) in comparison to the other STS subtypes. Additionally, responding patients who received beyond 6 cycles of trabectedin had significantly longer PFS (10.5 vs 5.3 months) and OS rates (33.4 versus 13.9 months) [53]. More recently, the first prospective phase IV trial evaluating the role of trabectedin in 218 patients with advanced STS among which 10% were chemotherapy-naïve showed a median PFS of 5.9 months with 6-month PFS of 49% and a median OS of 21.3 months. Additionally, ORR and DCR were 26.6% and 65.6% respectively with three patients achieving complete responses (1.3%). Trabectedin was very well tolerated with only 2.3% of febrile neutropenia and grade 3/4 toxicities were present in only 1.4% (nausea, neutropenia and pneumonia). Only one patient had grade 3 liver toxicity and there were no treatment-related deaths. 124 patients (56.9%) received 6 cycles or more of trabectedin and up to 44 cycles which confirms the good tolerance of the drug and the ability of administration for long periods of time [54]. Generally, trabectedin is well tolerated and can be administered continuously without cumulative toxicities in contrast to other STS regimens including doxorubicin and ifosfamide [18,55]. Trabectedin-related adverse events usually manifest by reversible grade 3/4 increase in hepatic transaminases and hematological toxicity [44,56]. It is safely administered in the frail population as adverse events are transient and generally manageable with dose reductions or administration delays [57].

Future perspectives for trabectedin in MLS

Promising data demonstrated a high activity for trabectedin in MLS patients however solid data remains inexistent in view of the small sample size of MLS patients included in the prospective studies. As such, it would of interest to validate markers of response to trabectedin. Active efforts are ongoing to identify prognostic and predictive factors of response to trabectedin. The GEIS-20 study group has identified two genes implicated in cell signaling, p53 and FAS, of the primary tumor as poor prognostic features [51,77]. Features of the microenvironment such as the presence of M1 infiltrating macrophages is associated with poorer response to trabectedin in MLS patients [78]. The genes implicated in cellular repair, CLU4A and ERCC1, are highly predictive of trabectedin response [79]. A prognostic model called GEISTRA including free interval between diagnosis and distant relapse, histological subtype and performance status classified patients between good and poor responders to trabectedin according to survival outcomes ranging between 2.5 and 25.7 months [80]. Moreover, it would be of value to evaluate the different patterns of radiological response of MLS to trabectedin as different modalities are emerging. The first are the CHOI criteria, based on the density measurement by the CT-scan contrast enhancement, showed an advantage over the current standard RECIST criteria in identifying responding patients [81]. The second is the growth modulation index (GMI), a method developed by Van Hoff in 1998, that consists in the use of successive time to progression in the same patient where he becomes his own control [82]. It is a metric of clinical benefit assessment in sarcoma patients defined by the ratio of the Time To Progression with the later line (TTPn) divided by the TTP of the previous line (n − 1). A GMI above 1.33 was associated with better oncological outcomes for STS patients treated with trabectedin [83].

Conclusion

This report demonstrates a particular activity for trabectedin in MLS patients despite the limitations inherent to the present data thus halting a solid proof of efficacy. The available studies have included MLS with other mediocre STS which may have blunted the efficacy of trabectedin. Moreover, the evaluation modalities are not standardized for an optimal radiological evaluation. In general, based on all available data, trabectedin seems to have consistent results with tolerable safety profile although real-life studies reported mixed outcomes. Based on the current standards for drug approvals, rare cancers represent a serious dilemma and should be accorded higher levels of uncertainty for eventual decision making. The increased number of patients that is required to achieve reliable outcomes represents a serious limitation to the validation of new treatments and could be avoided by performing low-power randomized trials. Lack of precise data on prior and current systemic and local treatments as well as standardized imaging methods limits a comprehensive analysis. Questions concerning the use of prognostic scores and predictive markers to trabectedin in MLS need to be answered. Answering these questions would hopefully provide more insights into the position of trabectedin in MLS.

Table 4
Real-life experience with trabectedin in soft tissue sarcomas.

Study	Year	N	Study design	Disease setting	ORR (%)	CR (%)	DCR (%)	PFS (Months)	OS (Months)	Toxicity (Grade 3/4)	Dose modifications
Buonadonna et al. [54]	2017	218	Retrospective	All lines in STS/1st (10%)	26.6	1.4	65.6	5.9	21.3	Febrile Neutropenia 2.3%	NA
Verret et al. [58]	2017	6	Retrospective	≥2 lines in DSRCT	0.0	0.0	33.3	1	4	Overall 67%	NA
Angarita et al. [59]	2016	77	Retrospective	≥2 lines in STS	14.1	0.0	37.9	1.3	6.7	Liver toxicity 18.7% Neutropenia 42%	DC 10%
Daupin et al. [60]	2016	45	Retrospective	All lines in STS/1st (17%)	37.8	8.9	59.8	4	9.1	Liver toxicity 24% Thrombocytopenia 20%	DC 15%
San Filippo et al. [61]	2015	61	Retrospective	≥2 lines in Synovial Sarcoma	15.0	0.0	50.0	3	NA	NA	NA
De Sanctis et al. [62]	2015	72	Retrospective	≥2 lines in STS	13.0	0.0	50.7	2.97	16.5	Liver toxicity 8.3% Neutropenia 9.6%	DC 2.8% DR 23.6%
Lecesne et al. [18]	2015	885	Retrospective	≥2 lines in STS	17.0	0.0	67.0	4.4	12.2	Liver toxicity 4% Neutropenia 35%	DR 48%
Khalifa et al.[63]	2015	11	Retrospective	≥2 lines in STS	9.1	0.0	81.8	11.6	22.3	Liver toxicity 27.3%	DR 18.2
Schak et al. [64]	2014	117	Retrospective	All lines in STS/1st (5%)	6.0	0.0	58.0	3	NA	Liver toxicity 22%	DC 18%
Ploner et al. [65]	2013	101	Retrospective	All lines in STS	12.0	3.0	NA	3.9	10.2	Liver toxicity 2.9/2.9%	NA
Schur et al. [66]	2013	60	Retrospective	All lines in STS/1st (8.3%)	NA	NA	NA	2.2	11.8	Liver toxicity 1.7% Leukopenia 15%	DR 11.7% DC 0
Samuels et al. [67]	2013	1895 (807)	Retrospective	≥2 lines in STS	5.0	0.5	43.0	NA	11.9	Liver toxicity 11% Neutropenia 9.6%	DR 40%
Blay et al. [53]	2013	181	Retrospective	All lines in STS/1st (6%)	10.0	0.0	49.0	3.6	16.1	NA	NA
Hoiczik et al. [68]	2013	101	Retrospective	≥2 lines in STS	NA	NA	NA	2.1	NA	Liver toxicity 4% Neutropenia 35%	DR:12.9%
Lecesne et al. [22]	2012	81	Retrospective	All lines in TRS/1st (1.2%)	10.0	0.0	59.0	4.1	17.4	Liver toxicity 39–47% Neutropenia 35%	NA
Banerjee et al. [69]	2011	133	Retrospective	≥2 lines in STS	10.0	0.0	52.0	2.23	5.1	Overall : 55%	DR 25%
Chahine et al. [70]	2011	15	Retrospective	≥2 lines in STS	0.0	0.0	33.3	NA	NA	NA	NA
Schmitt et al. [71]	2010	25	Retrospective	≥2 lines in STS	4.8	0.0	48.0	3.7	8.8	Liver toxicity 4% Neutropenia 8%	DC 0%
Kim et al. [72]	2010	21	Retrospective	≥2 lines in STS	4.8	0.0	38.0	2	NA	Liver toxicity 15% Neutropenia 35%	DR 33%
Shmerling et al. [73]	2010	35 (26)	Retrospective	≥2 lines in STS	7.6	0.0	57.7	4.27	NA	Liver toxicity 3.8/3.8%	NA
Fayette et al. [74]	2010	92	Retrospective	All lines in STS/1st (6%)	10.0	0.0	36.0	2.2	8.9	Liver toxicity 37% Neutropenia 42%	DR 32% DC 8%
Mohan et al. [75]	2008	88 (80)	Retrospective	All lines in TRS/1st (21%)	9.0	0.0	55.0	NA	NA	Liver toxicity 17% Neutropenia : 30%	NA
Demetri et al. [15]	2008	270	Prospective phase 2 randomized	≥2 lines in STS (Two different schedules of trabectedin)*	5.6 (A) vs 1.6 (B)	NR	NR	3.3 (A) vs 2.3 (B)	13.9 (A) vs 11.8 (B)	Neutropenia: 47% (A) and 21% (B) Liver Toxicity: 47% (A) and 14% (B)	DC: 6.2% (A) and 3.1% (B)
Roylance et al. [76]	2007	21	Retrospective	≥2 lines in STS	14.0	0.0	52.0	5.6	11.6	Liver toxicity 43% Neutropenia 48%	DR:0
Yovine et al. [38]	2004	54	Prospective phase 2	≥2 lines in STS (single arm)	3.7	0.0	39	1.9	12.8	Liver toxicity 50% Neutropenia 61%	DC: 7.4
Delaloge et al. [39]	2001	29	Prospective phase 1	≥2 lines in STS	14	0	55	2.8	7.8	Liver toxicity 24% Neutropenia 32%	DR 24% DC 0%

CR: complete response; DC: Discontinuation due to toxicity; DCR: disease control rate; DR: dose reduction; N: number of patients; NA: not available; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; STS: soft tissue sarcoma; DSRCT: Desmoplastic small round cell tumors.

* (A) 1.5 mg/m^2 in 24hr infusion or (B) 0.58 mg/m^2 weekly (3 weeks for 4-week cycle).

Conflicts of interest

None

Acknowledgment

None.

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