Use of first-line trabectedin in advanced leiomyosarcoma: a review of clinical data and future perspectives

Nadia Hindi[1], Florence Duffaud[2], Giacomo Giulio Baldi[3], Patricia Pautier[4]

Abstract
Leiomyosarcomas (LMS) represent a large subgroup of soft-tissue sarcoma (STS) generally considered moderately sensitive to conventional chemotherapy. Single-agent doxorubicin is the standard first-line therapy for advanced non-selected STS, although combination with ifosfamide appears to be superior in terms of objective response. Gemcitabine-based regimes, dacarbazine, trabectedin and pazopanib seem to be especially active in patients with advanced LMS, while the activity of ifosfamide in this histotype is low. Data derived from clinical trials and retrospective series show that trabectedin is especially active in L-sarcomas including non-gynecological and uterine LMS as well as liposarcomas, in particular myxoid liposarcomas. Trabectedin has also been tested in the first-line setting, alone or in combination with doxorubicin, for the treatment of LMS of uterine and non-uterine origin in a trial by the French Sarcoma Group (phase II study *LMS-02*) with encouraging results in terms of median progression-free survival and objective response. The toxicity profile of trabectedin appears to be comparable to, or even more manageable than, that of other chemotherapy combinations in the first-line setting. Designing new clinical trials based on specific histologic subtypes is feasible, and the results of such studies would help to optimize the management of patients with STS.

Key words: leiomyosarcoma, soft tissue sarcoma, trabectedin

Introduction

Soft-tissue sarcomas (STS) are a heterogeneous group of more than 50 different tumor subtypes, representing about 2% of all solid tumors in adults [1], with about 5 new cases per 100,000 each year in Europe [2]. Leiomyosarcomas (LMS) form a large subgroup of STS (about 24%) [3]. Although gene expression patterns have been reported to differ between uterine (uLMS) and non-uterine LMS, both are generally considered moderately sensitive to conventional chemotherapy [4].

STS can arise at any site in the body, and surgery (with adjuvant radiotherapy when indicated) is the mainstay of therapy when disease is localized [5]. Patients with high-risk sarcoma (high-grade, deep, >5 cm) [6], and those with tumors arising in the limbs or trunk wall [7] might benefit from adjuvant chemotherapy. Despite optimal local treatment, about one-third of the patients with STS develop metastasis and die as a result of their disease (with median overall survival [OS] of 14–18 months and median progression-free survival [PFS] of 4–7 months for patients treated with anthracycline-containing first-line regimens) [8].

Anthracycline-based regimens (mainly in combination with ifosfamide) have been the mainstay of systemic STS therapy over the last thirty years, being used in the adjuvant setting when indicated and for first-line treatment of advanced disease [9]. Other agents have also shown activity in sarcoma, and several options have been assessed in the setting or progression after anthracyclines in advanced STS. These include gemcitabine combinations, trabectedin and pazopanib. Regarding the different second-line options, expected PFS is about 2–5 months in most cases and there is a lack of direct comparison between the majority of options. Gemcitabine combinations (with docetaxel [10-12] or dacarbazine [13]) represent an interesting therapeutic option

[1]Medical Oncology Department, "Virgen del Rocio" University Hospital, Seville, Spain.
[2]Medical Oncology Department, La Timone University Hospital, Marseille, France.
[3]Medical Oncology Unit, "Santo Stefano" Hospital, Prato, Italy.
[4]Medical Oncology Department, Institute Gustave Roussy, Villejuif, France.
Correspondence to: Patricia Pautier, MD,
Medical Oncology Department, Institute Gustave-Roussy,
94805 Villejuif Cedex, France.
Phone: +33 1421 14211 – Fax: +33 14211 5214
E-mail: patricia.pautier@gustaveroussy.fr
CANCER BREAKING NEWS 2016;4(1):6-10
DOI: 10.19156/cbn.2016.0002

in patients with pretreated STS, especially in LMS, and probably also in other subtypes, such as undifferentiated pleomorphic sarcoma. Pazopanib was shown to increase PFS by 3 months compared with placebo in patients with non-adipocytic advanced STS [14]. Where clinical trial data are lacking, patient comorbidities and preferences, toxicity profile and histologic subtype are useful criteria to select further lines of therapy beyond anthracyclines and ifosfamide.

First-line therapy of metastatic STS: where are we?

At present, single-agent doxorubicin is the standard first-line therapy in advanced non-selected STS. Until now, phase III studies have not formally demonstrated the superiority of multiagent chemotherapy over doxorubicin alone in terms of OS in advanced disease [8, 9]. However, the combination seems to be superior in terms of response, being a valuable option when tumor shrinkage is needed to palliate symptoms or to facilitate surgery. The combination of gemcitabine and docetaxel, which showed activity in pretreated STS in phase II trials [10-12], was also tested as first-line therapy metastatic uLMS [15]. In this population, more than one-third of patients experienced an objective radiological response. However, recently, the GeDDiS phase III study did not show any superiority of first-line gemcitabine-docetaxel over doxorubicin alone either in terms of PFS or OS in advanced non-selected soft-tissue sarcoma [16].

Trabectedin is another active drug in STS [17, 18], and it has been evaluated in comparison with doxorubicin monotherapy for the first-line treatment of metastatic non-selected STS in the TRUSTS trial. Two schedules of trabectedin were assessed (1.3 mg/m^2 given over 3 hours and 1.5 mg/m^2 as a 24-hour continuous infusion, both given on day 1 every 3 weeks). Neither trabectedin regimen showed superiority over doxorubicin in this unselected population. Trabectedin interferes with DNA transcription by binding covalently to the DNA minor groove, interfering with transcription factors. Many sarcomas are characterized by genetic translocations resulting in fusion proteins, which could work as transcription factors. Trabectedin has been evaluated *versus* doxorubicin-based chemotherapy in the first-line of translocation-related sarcomas (TRS). Although underpowered, neither agent showed superiority over the other as first-line treatment in this population [19].

Combinations of doxorubicin with targeted therapies have also been assessed. Conatumumab, an antibody targeting and activating the proapoptotic protein TRAIL, did not improve patient outcome when added to doxorubicin [20]. Recently, a phase II randomized trial of the combination of doxorubicin and olaratumab, a monoclonal antibody targeting platelet-derived growth factor receptor (PDGFR), showed a trend towards better PFS compared with doxorubicin alone, and a statistically significant and clinically relevant improvement in OS (nearly 12 months) [21]. An ongoing phase III is being conducted to confirm these encouraging results [22]. Overall, though, at present there is no solid evidence for the superiority of an alternative to single-agent doxorubicin in non-selected STS.

Personalized treatment based on histologic subtype. Is it possible?

As noted previously, STS are a heterogeneous group of malignancies. Due to the low incidence of these diseases, clinical trials have traditionally included patients with several histologic subtypes. However, differential sensitivity to chemotherapy has been noted between the different histologic subtypes, something that should be taken into account in decision-making algorithms [23]. As examples of this, synovial sarcoma seems to be sensitive to high-dose ifosfamide [24, 25], angiosarcomas are sensitive to taxanes [26], dacarbazine and temozolomide seem to be particularly active in LMS [27]. Gemcitabine-based regimes seem to be especially beneficial in patients with LMS and undifferentiated pleomorphic sarcoma [10-13]. Trabectedin has shown potential in LMS, liposarcoma and synovial sarcoma [17, 28], and high activity has been described in myxoid liposarcoma [29]. Identifying differential sensitivity of the different histologic subtypes could help to optimize patient management by allowing physicians to choose the most appropriate sequence of drugs and design potential combinations to maximize the benefits obtained from systemic therapy.

Trabectedin and LMS

Use of trabectedin in patients with STS is associated with low response rates (usually <10% in pretreated patients [17, 28]). However, 3- and 6-month progression-free rates (39–56% and 24–37%, respectively) [17, 28-30] show that patients who do achieve disease stabilization could have a prolonged disease control. Data from clinical trials show better activity in some histologic subtypes, as LMS. In a phase II EORTC trial, 56% of patients with pretreated LMS achieved disease control with trabectedin 1.5 mg/m^2 given as a 24-hour continuous infusion. Data from the trabectedin expanded access program showed a 7.5% response rate in pretreated LMS, with a median OS of 16.2 months [31]. Of note,

trabectedin had a manageable toxicity profile, with neutropenia and elevation of transaminases being the most reported grade 3-4 toxicities; cumulative toxicities were not observed. Regarding the duration of therapy with trabectedin, a phase II trial from the French Sarcoma Group (T-DIS study) randomized patients with non-selected advanced STS achieving disease control after 6 cycles of trabectedin to continue or interrupt therapy; patients progressing after stopping trabectedin were allowed to restart the drug. After randomization, PFS at 6 months was 51.9% in the continuation group *versus* 23.1% in the interruption group (p=0.02) [32].

Trabectedin as first-line therapy for LMS: initial results and perspectives

Trabectedin has also been studied as first-line therapy for STS. A phase II trial assessing trabectedin 1.5 mg/m² infused over 24 hours in chemotherapy-naïve patients reported a clinical benefit rate of 20%. Interestingly, patients who had longer PFS times had LMS (PFS of 36 and 29+ months) [33]. Focusing on uLMS, the Gynecologic Oncology Group (GOG) enrolled 20 chemotherapy-naïve patients in a phase II trial with trabectedin 1.5 mg/m² (24-hour infusion). Two patients (10%) achieved a partial response, and median PFS and OS were 5.8 months and >26 months respectively [34]. Although the objective response rate remained low, outcomes are similar to those reported with other regimens in the first-line setting [8, 15, 35].

Combinations of trabectedin have also been tested. Based on preclinical data showing a synergistic antitumor effect of doxorubicin and trabectedin and the safety of the combination in two phase I trials [36, 37], a phase II trial was performed by the French Sarcoma Group [38]. This trial enrolled 109 chemotherapy-naïve patients with advanced LMS (47 uterine and 61 soft-tissue). Patients received up to 6 cycles of doxorubicin 60 mg/m² followed by trabectedin 1.1 mg/m² infused over 3 hours; these doses and schedules were based on those used in a previous phase I trial [38]. The phase II study reported striking results in terms of median PFS (8.2 months for uLMS and 12.9 months for soft-tissue LMS) and objective response rate (59.6% and 39.4% for uLMS and soft-tissue LMS respectively). About 90% of patients (87.2% with uLMS and 91.8% with soft-tissue LMS) achieved disease control. Median OS for uterine and soft-tissue LMS patients was 20.2 and 34.5 months, respectively [38]. Regarding toxicity, the most frequent grade 3-4 adverse events were neutropenia (78% of patients), elevation of transaminases (39%), thrombocytopenia (37%), anemia (27%), febrile neutropenia (24%), and fatigue (19%). One toxic death was reported. Overall, this toxicity profile seems to be comparable to or even more manageable than other combinations such as doxorubicin and ifosfamide [8] or gemcitabine and docetaxel [10].

On the other hand, a randomized phase II trial by the Spanish Group for Research on Sarcoma (GEIS) comparing trabectedin-doxorubicin *versus* doxorubicin alone failed to find any difference between outcomes in patients treated with trabectedin + doxorubicin *versus* doxorubicin alone [39], although this study included patients with different histologic subtypes.

Given the results of the LMS-02 and T-DIS trials, it would appear that a phase III clinical study comparing the combination of trabectedin and doxorubicin to doxorubicin alone for the first-line treatment of metastatic LMS is warranted. The continuation of trabectedin beyond 6 cycles in patients achieving disease control could also be explored in this setting.

Conclusions

STS is a heterogeneous group of malignancies with different biologic behaviors, including differential sensitivity to the active systemic drugs. Developing clinical trials based on specific histologic subtypes is feasible, and extremely useful for facilitating the optimal management of patients with STS. The combination of trabectedin and doxorubicin in LMS of both uterine and non-uterine origin appears to be a promising option that provides clinically meaningful benefit. This approach deserves further investigation in a phase III prospective randomized clinical trial.

Acknowledgments

The authors thank Nicola Ryan, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

References

1. Fletcher CDM, Bridge JA, Beidge JA, et al. WHO classification of tumours of soft tissue and bone. Lyon, Fr IARC. 2013.
2. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer 2013;49(3):684-95.
3. Ducimetière F, Lurkin A, Ranchere-Vince D, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS One 2011;6:e20294.
4. Skubitz KM, Skubitz APN. Differential gene expression in leiomyosarcoma. Cancer 2003;98(5):1029-38.
5. Working ESN. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii102-12.
6. Pervaiz N, Colterjohn N, Farrokhyar F, et al. systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113(3):573-81.
7. Frustaci BS, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles : results of the Italian randomized cooperative trial. J Clin Oncol 2001;19(5):1238-47.
8. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014;15(4):415-23.
9. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first- line treatment of advanced soft tissue sarcomas: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995;13(7):1537-45.
10. Hensley ML, Blessing JA, Degeest K, et al. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol Oncol 2008;109(3):323-8.
11. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: A Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group (TAXOGEM study). Oncologist 2012;17(9):1213-20.
12. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas : results of Sarcoma Alliance for Research Through Collaboration study 002. J Clin Oncol 2009;25(19):2755-64.
13. García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol 2011;29(18):2528-33.
14. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379(9829):1879-86.
15. Hensley ML, Blessing JA, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: A Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008;109(3):329-34.
16. Seddon BM, Whelan J, Strauss SJ, et al. GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). J Clin Oncol 2015;33:(Suppl):abstr 10500.
17. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group trial. J Clin Oncol 2005;23(3):576-84.
18. Demetri GD, Chawla SP, Von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: Results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27(25):4188-96.
19. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer 2014;50(6):1137-47.
20. Demetri GD, Le Cesne A, Chawla SP, et al. First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: a phase I/II open-label and double-blind study. Eur J Cancer 2012;48(4):547-63.
21. Tap WD, Jones RL, Chmielowski B, et al. A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor α (PDGFRα) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). J Clin Oncol 2015;33:(Suppl):abstr 10501.
22. http://www.clinicaltrials.gov. A study of olaratumab (LY3012207) in participants with advanced soft-tissue sarcoma (NCT02659020).
23. Casali PG. Histology- and non-histology-driven therapy for treatment of soft tissue sarcomas. Ann Oncol 2012;23(Suppl 10):x167-9.
24. Rosen G, Forscher C, Lowenbraun S, et al. Synovial sarcoma: Uniform response of metastases to high dose ifosfamide. Cancer 1994;73(10):2506-11.
25. Le Cesne A, Antoine E, Spielmann M, et al. High-dose ifosfamide: Circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol 1995;13(7):1600-8.
26. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: The ANGIOTAX study. J Clin Oncol 2008;26(32):5269-74.
27. Garcia del Muro X, Lopez-Pousa A, Martin J, et al. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. Cancer 2005;104(8):1706-12.
28. Yovine A, Riofrio M, Blay JY, et al. Phase II study of ectein-

ascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004;22(5):890-9.
29. Grosso F, Jones RL, Demetri GD, et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas : a retrospective study. Lancet Oncol 2007;8(7):595-602.
30. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34(8):786-93.
31. Samuels BL, Chawla S, Patel S, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: Results of a worldwide expanded access program study. Ann Oncol 2013;24(6):1703-9.
32. Le Cesne A, Blay JY, Domont J, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol 2015;16(3):312-9.
33. Garcia-Carbonero R, Supko JG, Maki RG, et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. J Clin Oncol 2005;23(24):5484-92.
34. Monk BJ, Blessing JA, Street DG, et al. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a Gynecologic Oncology Group study. Gynecol Oncol 2012;124(1):48-52.
35. Oosten AW, Seynaeve C, Schmitz PIM, et al. Outcomes of first-line chemotherapy in patients with advanced or metastatic leiomyosarcoma of uterine and non-uterine origin. Sarcoma 2009;2009:348910.
36. Blay JY, von Mehren M, Samuels BL, et al. A phase I combination study of trabectedin and doxorubicin in patients with soft tissue sarcoma. Clin Cancer Res 2008;14(20):6656-62.
37. Sessa C, Perotti A, Noberasco C, et al. Phase I clinical and pharmacokinetic study of trabectedin and doxorubicin in advanced soft tissue sarcoma and breast cancer. Eur J Cancer 2009;45(7):1153-61.
38. Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol 2015;16(4):457-64.
39. Martin-Broto J, Lopez-Pousa A, Garcia del Muro X, et al. Randomized phase II trial of doxorubicin vs. trabectedin plus doxorubicin in first line treatment of patients with advanced non-resectable or metastatic soft tissue sarcomas: a Spanish Group for Sarcoma Research (GEIS) study. Eur J Cancer 2013;49(Suppl 2):S875.