



Review

Systemic chemotherapy of advanced soft tissue sarcomas

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ARTICLE INFO

Article history:

Received 15 January 2017

Received in revised form

12 April 2017

Accepted 1 May 2017

Available online 15 May 2017

Keywords:

Soft tissue sarcoma

Metastatic

Chemotherapy

ABSTRACT

Soft tissue sarcomas, which originate from the mesenchymal tissue, represent a rare disease group with more than 100 subtypes. Primary treatment is surgical excision. In locally-advanced or metastatic cases, systemic treatment is the only therapeutic approach. Because of their heterogeneity, prognosis and response to the chemotherapy may be relatively different. Monotherapy with doxorubicin and its combination with ifosfamide continue to be the standard approach in the first-line treatment of advanced disease. Histology-directed therapy has become popular with the introduction of novel cytotoxic agents. Successful results have been achieved with recent developments in the field. Currently, the median overall survival rate in advanced stage disease barely exceeds 12 months in spite of the novel treatment options. In this review, our objective was to summarize the current data on cytotoxic treatments in the metastatic soft tissue sarcomas.

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1. Introduction

Soft tissue sarcomas (STS) are rare tumors originating from the mesenchymal tissue. They constitute less than 1% of all malignancies seen in adults.¹ According to the database of the American Cancer Society, an estimated 12,310 new cases and 4990 deaths due to STS were expected in the United States in 2016.¹ STS are a rather heterogeneous disease group. Updated WHO classification identified approximately 100 entities with different clinicopathological and genetic characteristics in 12 different sections.²

Surgery is the standard therapy in localized STS. In selected cases, adjuvant radiotherapy and chemotherapy might be combined with surgery. Disseminated disease develops in roughly half of the patients with early stage STS who received curative treatment and these patients eventually succumb to their disease.^{3,4} Systemic therapy is the primary treatment for unresectable locally-advanced and metastatic disease. In metastatic sarcomas, expected average survival is approximately 12 months and the 2-year survival rate is 20% with current treatment options.³ The goal of systemic therapy is to increase overall survival (OS), shrink

the tumor mass and palliate the symptoms rather than achieving a cure. We intend to give a brief synopsis of systemic chemotherapy options in advanced STS.

2. Chemotherapy in metastatic soft tissue sarcomas

Several chemotherapeutic agents were tested in the treatment of metastatic STS in the last 50 years.⁵ Doxorubicin, ifosfamide, gemcitabine and dacarbazine were the main agents with modest efficacy. Although these agents are effective as monotherapy, they are usually used as a component of the combination regimens.

2.1. Monotherapy

Anthracyclines are the main agents used in the first-line therapy of metastatic STS. There have been several phase II and III studies evaluating the efficacy of doxorubicin monotherapy in comparison with other agents. In these studies, objective response rates (ORR) of 9–30%, median time to progression (TTP) of 3.7–6 months, median progression-free survival (PFS) of 2.5–6.5 months and median OS of 8–17 months were reported.^{5–10} Van Glabbeke et al. conducted a meta-analysis evaluating the efficacy of first-line doxorubicin treatment in 2185 metastatic STS patients. ORR was 26% and OS was 51 weeks.³ Doxorubicin has become the standard agent in the first-line treatment of metastatic sarcomas based on these studies. Recommended doxorubicin dose is 75 mg/m² every 3

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Peer review under responsibility of Turkish Society of Medical Oncology.

weeks for a maximum of 6 cycles because of increased response rate with higher dose and cumulative risk of cardiotoxicity.⁵

Because of dose-limiting cumulative cardiotoxicity despite its efficacy, other anthracyclines besides doxorubicin have been tested in the treatment of metastatic STS. Epirubicin yielded comparable ORR, survival and cardiotoxicity rates.^{9–11} In a study utilizing the same doxorubicin and epirubicin dose (75 mg/m²), ORR (18% vs. 25%) and median OS (10.3 vs. 12 months) were comparable with lower cardiotoxicity ($p = 0.04$) in the epirubicin group. However, usual epirubicin dose is higher than that in routine clinical practice.⁹ In phase II studies, pegylated liposomal doxorubicin (PLD) induced an ORR of 0–12% with no cardiotoxicity.^{12–14} In a randomized phase II EORTC trial, 94 patients with treatment-naïve metastatic STS were randomized to doxorubicin versus PLD. ORR was comparable in both groups (9% and 10%), but adverse events differed.¹⁵ Cardiotoxicity was more common in doxorubicin group (4 patients vs none) while hand-foot syndrome was more prominent in PLD group (25 patients vs none). In conclusion, anthracyclines have similar efficacy in metastatic STS with different side effect profiles.

Ifosfamide is an important agent with demonstrated efficacy in the metastatic STS. First-line phase II studies showed ORR of 10–38% with 6–11 months median duration of response.^{16–18} In an EORTC phase III study, 326 STS patients were enrolled to compare standard-dose doxorubicin (75 mg/m² q3wk) with 2 different schedules of ifosfamide (3 g/m²/day bolus on days 1–3 or 9 g/m² continuous infusion over 3 days) as first-line therapy. In all three groups, comparable results for PFS (2.5 vs. 2.1 vs. 3 months, respectively) and ORR (11.8%, 5.5%, 8.4%, respectively) were reported.⁷ Based on these results, doxorubicin remains the treatment of choice in the first-line setting.

In the second-line treatment of patients who failed doxorubicin, 7–41% ORRs were achieved in phase II ifosfamide monotherapy studies using standard and high-dose regimens (<10 g/m²/cycle vs. >10 g/m²/cycle).^{17–23} ORR and OS were 7–26% and 6.5–12 months with standard dose versus 16–41% and 13–18 months with high dose, respectively.^{17–23} There is no head-to-head comparison of standard-dose vs. high-dose ifosfamide regimens. Although, higher doses with daily bolus schedule have been proposed to lead to higher ORR, there is no randomized study.^{19,20} In another study, third-line high dose ifosfamide was reported to induce 39% ORR and 13 months median OS in patients treated with standard-dose ifosfamide in the second-line setting.²⁴ Salvage high-dose ifosfamide might be a viable option in patients who received prior standard-dose ifosfamide.

Several other agents including gemcitabine,^{25–27} vinorelbine,^{28,29} methotrexate,³⁰ dacarbazine,^{31,32} cisplatin,³³ carboplatin,³⁴ and temozolomide³⁵ were also tested in the treatment of STS showing limited single-agent efficacy with ORR <20%.

2.2. Combination chemotherapy

Multiagent combination chemotherapy with CYVADIC (cyclophosphamide, vincristine, doxorubicin and dacarbazine) had been considered standard therapy for several decades.³⁶ Several studies investigating efficacy of combination schedules in metastatic STS failed to demonstrate a significant survival advantage over monotherapy with doxorubicin. Therefore, the debate continues as to whether to prefer combination over monotherapy in routine clinical practice.

Studies comparing doxorubicin monotherapy with doxorubicin + ifosfamide combination showed response rates of 20–24% and 28–34%, respectively. Although the survival rates were comparable, myelosuppression was significantly higher in the combination group.^{36–40} EORTC Sarcoma Group (EORTC STBSG)

analysis evaluated doxorubicin monotherapy ($n = 660$) versus ifosfamide as monotherapy ($n = 414$) or in combination with doxorubicin ($n = 923$).⁴⁰ OS rates were comparable in patients receiving doxorubicin monotherapy and combination therapy ($p = 0.129$). But PFS (4.5 vs. 3.5 months; $p = 0.044$) and ORR were higher in the combination therapy group. Analysis of patients treated with ifosfamide-based therapy revealed significantly longer PFS in the combination group compared to monotherapy (5.5 vs. 2.5 months; $p < 0.0001$). In this review, good physical condition, female gender, low histological grade, primary localization in extremities and absence of the distant metastasis were independent prognostic factors predicting OS.⁴⁰

A large randomized controlled phase III EORTC study allocated 453 metastatic STS patients to doxorubicin monotherapy versus doxorubicin + ifosfamide combination in the first-line therapy.⁴¹ PFS (7.4 vs. 4.6 months, HR = 0.74, $p = 0.003$) and ORR (%26 vs %14, $p < 0.0006$) were significantly higher in the combination group. However, there was no difference in OS (12.8 vs. 14.3 months; HR = 0.83, $p = 0.076$). Grade 3–4 hematological toxicities were significantly higher in the combination group.⁴¹

Available data showed that although the doxorubicin + ifosfamide combination was more toxic compared to the doxorubicin monotherapy, the combination had better PFS and ORR results. It was suggested that the combination therapy should be preferred in selected patients with younger age, good physical condition, symptoms due to large tumor size and a chance of cure with additional treatment methods like surgery and radiotherapy.

Response rates of synovial sarcomas to ifosfamide-based regimens were better compared with the other STS subtypes. Rosen et al. treated 13 synovial sarcoma patients with ifosfamide and reported complete remission (CR) in 4 patients and partial remission (PR) in 9 patients. Nine of 13 patients had received doxorubicin in the first-line therapy.⁴² In a phase II study conducted by EORTC, 124 patients were treated with high-dose ifosfamide (12 g/m²) achieving an impressive 40% ORR in synovial sarcoma subgroup (8/18) whereas ORR in intent-to-treat population was only 18%.²⁰ In another phase III study, doxorubicin + ifosfamide combination induced a significantly higher ORR compared with doxorubicin monotherapy in synovial sarcoma patients (88% vs. 20%, $p = 0.02$).³⁸ Data regarding the ifosfamide efficacy in synovial sarcoma was usually obtained from subgroup analyses. Therefore, starting treatment with doxorubicin + ifosfamide combination seems to be an effective choice in synovial sarcoma patients. Although, ifosfamide is effective in the treatment of synovial sarcoma, it has a lower efficacy in leiomyosarcomas compared to the other histological subtypes.^{17–19}

Gemcitabine monotherapy has a limited efficacy in the treatment of metastatic STS (ORR 6–18% and OS 6–13.9 months).^{25–27} Combinations of gemcitabine with vinorelbine⁴³ and dacarbazine⁴⁴ provided higher response rates. Gemcitabine + docetaxel combination was clinically the most studied and the most effective combination among them. Our experience with second-line gemcitabine + docetaxel combination showed an ORR of 20.3% and a median OS of 18 months.⁴⁵ In a phase II randomized study of previously-treated patients, 49 patients received gemcitabine monotherapy and 73 received gemcitabine + docetaxel combination.⁴⁶ In the combination group, ORR (16% vs. 8%), PFS (6.2 vs. 3 months) and OS (17.9 vs. 11.5 months) were significantly better than the monotherapy group. In this study, subgroup analysis revealed that the combination therapy was more effective in leiomyosarcoma and undifferentiated pleomorphic sarcoma subtypes.⁴⁶ Ninety patients with previously-treated leiomyosarcoma including 46 patients with uterine leiomyosarcoma were included in TAXOGEM study to compare gemcitabine monotherapy with gemcitabine + docetaxel combination.⁴⁷ Although, there was no

significant difference between the groups in uterine leiomyosarcoma patients regarding ORR (24% vs. 19%) and PFS (4.7 vs. 5.5 months), combination therapy provided inferior ORR (14% vs. 5%) and PFS (3.8 vs. 6.3 months) in the non-uterine leiomyosarcoma group. OS results were comparable between the groups (23 vs. 20 months in uterine leiomyosarcoma group and 13 vs. 15 months in non-uterine leiomyosarcoma group).⁴⁷ In light of the results of these clinical trials, gemcitabine + docetaxel combination was recommended as the preferred treatment option in patients with tumor progression after the first-line doxorubicin-based therapy.

Preliminary results of the GeDDIS trial, in which doxorubicin was compared with gemcitabine + docetaxel combination in the first-line treatment of advanced STS patients, were presented in abstract form only.⁴⁸ In this study, 257 patients were equally randomized into two groups and progression-free survival rate (PFR) in 24th week was set as the primary endpoint. PFR was 46% in both groups. Median PFS (23 vs. 24 months; HR = 1.28) and median OS (71 vs. 63 weeks; HR = 1.07) were also comparable between groups. Because toxicity was higher in combination group and no OS advantage was demonstrated, the standard therapy remains unchanged.⁴⁸

3. Soft tissue sarcomas with specific histological characteristics

For decades, all STS have been treated with single agent chemotherapy because of their rarity and lack of experience regarding treatment of specific histological subtypes. STS have more than 100 histologically identified subtypes with well-defined clinicopathological characteristics and responses to treatment.

Over the years, effective novel cytotoxic agents have been introduced in the treatment of specific histological subtypes because of the understanding of the importance of histological subtypes determination coupled with accumulation of knowledge regarding these entities.^{49,50}

3.1. Trabectedin

Trabectedin exerts its cytotoxicity via its selective DNA binding properties. In early studies conducted with trabectedin, relatively low ORR (4–18%) were reported. In these studies, the ORR were higher with longer duration in leiomyosarcoma, myxoid liposarcoma and synovial sarcoma.^{51–54} Seventy-six pretreated patients with advanced stage translocation-related sarcomas were included in a phase II study to compare trabectedin with placebo. PFS was significantly longer in trabectedin patients (5.6 vs. 0.9 months, HR = 0.07, $p < 0.0001$).⁵⁵ Moreover, median OS was also longer with trabectedin (not reached vs. 8 months, HR = 0.42). In a dose-finding phase II study, 270 patients diagnosed with liposarcoma and leiomyosarcoma were evaluated in order to compare two different schedules (0.58 mg/m²/3 h infusion on days 1, 8 and 15 every 4 weeks vs. 1.5 mg/m²/24 h infusion every 3 weeks). Median TTP (3.7 vs. 2.3 months, HR = 0.73, $p = 0.03$) and median PFS (3.3 vs. 2.3 months, HR = 0.75, $p = 0.04$) results were superior in 24-hour infusion group every 3 weeks. Although, OS was also longer, the difference was statistically non-significant (13.9 vs. 11.8 months, HR = 0.84, $p = 0.19$).⁵⁶ We have observed a PFS of 3.75 months and OS of 15 months with trabectedin in a small sample of case series.⁵⁷ Trabectedin dose 1.5 mg/m²/24 h infusion every 3 weeks remains the preferred schedule in the second-line setting.

In a phase III randomized trial, 518 patients with metastatic liposarcoma and leiomyosarcoma, who had progressive disease (PD) after first-line treatment were evaluated in order to compare trabectedin with dacarbazine.⁵⁸ The administration schedule of trabectedin was 1.5 mg/m² every 3 weeks as a 24-hour infusion.

The primary endpoint was OS. Although the median PFS (4.2 vs. 1.5 months, HR = 0.55, $p < 0.001$) was superior in the trabectedin group, OS (12.4 vs. 12.9 months, HR = 0.87, $p = 0.37$) and ORR (10% vs 7%) were comparable. Clinical benefit rate (CBR=ORR + stable disease [SD]) was superior in trabectedin group (34% vs 19%).⁵⁸ Based on these results, the US Food and Drug Administration (FDA) has approved to trabectedin in the second-line treatment of advanced liposarcomas and leiomyosarcomas.

The therapeutic efficacy of the trabectedin + doxorubicin combination in the first-line therapy of the metastatic leiomyosarcoma was evaluated in a non-randomized, multi-center phase II study.⁵⁹ Overall 109 patients were enrolled in the study (47 uterine leiomyosarcomas, 61 non-uterine leiomyosarcomas). The CBR was 87.2% in the uterine leiomyosarcoma group (59.6% PR, 27.7% SD) and 91.8% (3.3% CR, 36.1% PR, 52.5% SD) in the non-uterine leiomyosarcoma group. OS was 34.5 months in non-uterine and 20.2 months in uterine leiomyosarcoma patients. Trabectedin + doxorubicin combination appears a promising first-line treatment alternative with an acceptable toxicity profile and high response rates.

Based on the available studies, trabectedin has become an effective alternative for the treatment of patients with L-type sarcomas (leiomyosarcoma and liposarcoma, especially myxoid liposarcoma) who showed tumor progression after the first-line therapy.

3.2. Eribulin

Eribulin is an inhibitor of microtubule assembly originally used in breast cancer patients. Based on its activity in preclinical studies, 128 metastatic STS patients who had received one line of combination therapy or 2 different agents as monotherapy, were evaluated in a multi-center phase II study.⁶⁰ The dose was 1.4 mg/m² on days 1 and 8, every 21 days. Twelve-week PFS was accepted as the primary endpoint of the study. The study achieved prespecified endpoint in 12 of 38 (31.6%) leiomyosarcoma, 15 of 32 (46.5%) liposarcoma and 4 of 19 (21%) synovial sarcoma patients. In 52% of patients grade 3–4 neutropenia (6% febrile neutropenia) were reported.⁶⁰

A multi-center, randomized phase III trial enrolled 446 patients with locally-advanced or metastatic liposarcoma and leiomyosarcoma to compare eribulin with dacarbazine. All the patients had failed at least 2 lines of treatment including anthracyclines. The primary endpoint of OS was significantly longer in the eribulin group (13.5 vs 11.3 months; HR = 0.75, $p = 0.01$). There was no significant difference between the groups regarding PFS and ORR. OS (15.6 vs. 8.4 months, HR = 0.51) and PFS (2.9 vs. 1.7 months, HR = 0.52) were longer in liposarcoma patients treated with eribulin. OS (12.8 vs. 12.3 months, HR = 0.90) and PFS (2.2 vs. 2.6 months, HR = 1.05) were comparable in leiomyosarcoma subgroup. Based on the results of this study, the FDA approved eribulin for metastatic or locally-advanced liposarcoma patients after anthracycline failure.⁶¹

3.3. Angiosarcoma

Angiosarcomas are rare STS of vascular origin. They are known to be refractory to the standard STS therapies with an aggressive clinical progress and a short survival period. In the phase II ANJIOTAX study, 30 patients were enrolled to evaluate the efficacy of weekly paclitaxel treatment in angiosarcomas.⁶² The primary endpoint was PFR after 2 cycles of the therapy. Two-month and 4-month PFR were 74% and 45%, respectively. Median TTP was 4 months and median OS was 8 months. PFR and OS were comparable regardless of previous chemotherapy use.⁶² In an EORTC

retrospective analysis of 32 angiosarcoma patients treated with weekly or every 3 weeks paclitaxel schedule, ORR was 62% in the whole series and 75% in the cutaneous forms. Median TTP was 7.6 months (range, 1–42).⁶³ In another retrospective analysis, weekly and every 3 week paclitaxel regimens were compared and weekly regimen was found more effective, especially for scalp angiosarcomas.⁶⁴ In a large French retrospective study, 117 metastatic angiosarcoma patients were analyzed to compare the efficacy of doxorubicin and weekly paclitaxel in the first-line treatment.⁶⁵ Objective responses were found to be more frequent in cutaneous angiosarcomas in the paclitaxel-treated group. Median OS was longer with weekly paclitaxel compared to doxorubicin (10.3 vs. 5.5 months, $p = 0.002$).⁶⁵ In a small-sized retrospective study with 13 patients, PLD ($n = 6$) was compared with paclitaxel ($n = 7$). In 3 of 6 patients treated with PLD, PR was observed for a duration of 6, 19 and > 20 months.⁶⁶ Five of 8 patients treated with paclitaxel experienced major responses (3 PR, 2 CRs). Paclitaxel and PLD both might be used effectively in the first-line or in the salvage therapy of metastatic angiosarcomas considering their favorable toxicity profile.

4. Conclusion

STS are rare and heterogenous group of tumors. Despite to enormous developments in the treatment of malignant neoplasms, little progress has been documented in sarcomas. In advanced disease, single-agent doxorubicin remains the gold standard in the first-line treatment. Combination of doxorubicin with ifosfamide induces greater response rates, albeit with a higher price and similar OS. Therefore, combination therapy should be preferred in fit patients who need tumor cytoreduction. The efficacy of gemcitabine + docetaxel combination is well known in the second-line treatment of advanced STS. Its efficacy is more prominent in patients with uterine leiomyosarcomas.

Histology-directed therapy has become popular with the introduction of novel cytotoxic agents. Trabectedin and eribulin are examples of new agents effective in advanced L-type sarcomas. Eribulin is approved for the treatment of liposarcomas only. Novel therapies with targeted agents have been under investigation. Pazopanib is the only approved tyrosine kinase inhibitor based on the phase 3 PALETTE trial.⁶⁷ Clinical trials of PD-1 inhibitors have shown promising results.

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