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Review

Systemic chemotherapy of advanced soft tissue sarcomas

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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.

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

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these studies. Recommended doxorubicin dose is 75 mg/m^2 every 3 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/m^2), 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/m^2 q3wk) with 2 different schedules of ifosfamide (3 g/m^2/day bolus on days 1–3 or 9 g/m^2 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/m^2/cycle vs. >10 g/m^2/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 temozolomide[35] 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/m^2) 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 vinorelbine[43] and dacarbazine[44] 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

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