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REVIEW ARTICLE

Systemic Therapy in Soft Tissue Sarcomas: Past, Present and Future

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Abstract Soft tissue sarcomas (STS) comprise 1% of all cancers diagnosed worldwide with more than 40 different histological subtypes each with distinct underlying biology, natural history and response to treatment. Due to the differential chemosensitivity it is imperative to have a correct histological diagnosis for optimal treatment of these patients. Even though surgery remains the primary modality of treatment there is increasing specialization of chemotherapy with respect to histological subtype. In general there is no place for "one size fits all strategy". To correctly define the role of chemotherapy, an extensive search was carried out online and offline for all relevant articles concerning chemotherapy in soft tissue sarcoma. This review aims to discuss the evolution of chemotherapy, its present role in neoadjuvant, adjuvant, metastatic settings and exciting trends with the advent of targeted therapies.

Keywords Soft tissue sarcoma · Adjuvant chemotherapy · Trabectedin

Introduction

Soft tissue sarcomas (STS) comprise a diverse group of rare tumors that constitute 1% of all cancers. It comprises of more than 40 different subtypes each with distinct underlying biology, natural history and response to treatment [1]. Thus the histological and molecular diagnostic accuracy is critical for optimal treatment of these patients. Chemotherapy for soft tissue sarcoma has evolved over the last two decades with some histological subtypes relatively more chemosensitive than the other. Earlier a clear role of cytotoxic agents like doxorubicin & ifosfamide was established in palliation of advance diseases only. The role of neoadjuvant and adjuvant chemotherapy remained controversial, however the recent metaanalysis for STS has shown an increase in overall survival with the combination of ifosfamide & doxorubicin, which is the standard of care now in adjuvant setting. In locally advanced and metastasis STS, adriamycin single agent is the preferred choice, ifosfamide in combination to adriamycin can be used for rapid control of symptoms in a patient with good performance status.

Apart from ewings sarcoma family of tumor (ESFT) and rhabdomyosarcoma for which chemotherapy is essential part of primary management there is increasing specialization of chemotherapy according to histological subtype such as taxanes for angiosarcomas, gemcitabine and docetaxel for leiomyosarcomas, malignant fibrous histiocytoma and recently approved drug trabectadin for advanced STS progressed on adriamycin and ifosfamide therapy. This review aims to discuss the evolution and role of chemotherapy in different histological subtypes.

Metastatic STS

Apart from chemosensitive tumors like Ewings sarcoma & rhabdomyosarcoma which are potentially curable even though metastatic, all other STS fare poorly with a median survival of 8–12 months. Even though a prior good local control is

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achieved, 50% patient eventually develop local recurrence or metastatic disease. Lung remains the most common site of distant metastasis specially in malignant fibrous histiocytoma, synovial sarcoma and leiomyosarcoma. Among these, patients with limited pulmonary disease have somewhat better survival with metastectomy (5 year survival 20–30%) than patients with unresectable disease.

In this group the goal of treatment is palliation of symptoms and improved quality of life. Chemotherapy remains the mainstay of treatment for these patients but one needs to consider the aggressiveness of treatment in order to avoid the potential toxicity. A decision whether combination chemotherapy is better than sequential administration of single agents should be taken after discussion with family members and need for immediate control of symptoms. Numerous drugs has been tried, but only anthracyclines (doxorubicin and epirubicin), alkylating agent (ifosfamide) and dacarbazine have proven to be effective.

Single Agents

Doxorubicin

It is used alone or in combination with other drugs. Single agent response rates are 20–30% with a median survival of 7.7–12 months [2]. It exhibits a dose response relationship so response rates increase with higher doses. Optimal responses have been seen with dosages in the range of 75–90 mg/m2. Pegylated liposomal doxorubicin can be used in patients where doxorubicin is contraindicated but response rates are much lower. Another anthracycline derivative, epirubicin has been tried without any substantial benefit. Main toxicities of anthracyclines agents are myelosuppression, G.I toxicity, alopecia and cardiotoxcity.

Ifosfamide

It belongs to alkylating class of antineoplastic agents and follows a dose response relationship similar to doxorubicin. It can be used as first line or second line along with adriamycin. Dose of 9–11 g/m2 every 3 weekly is recommended with no preferences for short infusions or continuous i.v infusion. Lorigan et al. in a phase 3 trial compared ifosfamide 9 g/m2 as a continuous infusion over 3 days to 3 g/m2 over 3 h with standard dose of doxorubicin repeated every 3 weekly. No difference was noted in terms of progression free survival & overall survival [3].

Dacarbazine

It has been studied most extensively and is used in combination with other drugs, doxorubicin, ifosfamide and mesna (MAID regime) in front line or as a salvage option later. Temozolomide, its oral equivalent appears to have similar response.

Combination Chemotherapy

Various combinations mostly doxorubicin based have been used to achieve higher responses (up to 45%), however duration of responses is shortlived in the range of 8–11 months. A recent metaanalysis that included 3 phase III trials & 23 phases II trials concluded that addition of ifosfamide improves the response rates at the cost of higher toxicity (grade 3 & 4 myelosuppression) without any difference in 1 year survival. All 3 phase III trials till date report a median survival of 8.4–13 months [4].

Neoadjuvant Chemotherapy

It has been tried alone or combined with radiotherapy. Other techniques used are isolated limb perfusion and hyperthermic chemotherapy. Neoadjuvant chemotherapy offers the advantage of downsizing the tumor so as to increase the rate of limb salvation, secondarily it acts as a surrogate marker of chemosensitivity of disease.

Concurrent use of chemoradiation with agents like doxorubicin at a dose of 12 mg/m2/day by Toma et al. demonstrated a partial response rate of 56% and a complete response of 11%. Subsequent studies have used 20 mg/m2/week of doxorubicin and reported a good surgical clearance. Use of EBRT (44 Gy) with MAID protocol has demonstrated a superior disease free survival, overall survival as compared to historical controls. However, both these studies were hampered by high rates of wound complications precluding its use outside a clinical trial [5].

At this time benefit of induction chemotherapy remains uncertain due to limited randomized trials. There has been only one randomized phase II study EORTC, STBCG 62871 that compared three cycles of 3 weekly doxorubicin (50 mg/m2) and ifosfamide (5 g/m2) with surgery or alone in high risk potentially resectable STS. High risk tumors were defined as size >8 cm, grade 2/3(less than 8 cm) or grade 2/3 locally recurrent tumor. At a median follow up of 7.3 years disease free survival and overall survival were not significant (52% versus 56%) and (64 versus 65%) respectively [6]. Another trial by EORTC group addressed the role of neoadjuvant chemotherapy (etoposide, ifosfamide and doxorubicin) with hyperthermia. Patients included had tumors with size >5 cm, grade 2/3, deep with extracompartmental and recurrent sarcoma. Overall response rate was higher in hyperthermia group (28.7% versus 12.6%) with higher median PFS (45.3% versus 23.7%) [7].

Extrapolating from the data in melanoma, isolated limb perfusion with TNF-alpha (Tumor necrosis factor alpha) has shown encouraging results in a few case series. TNF-alpha increases the vascular permeability of cytotoxic drugs. Eggermont A.M et al. [8] demonstrated an overall response rates of 76% and a limb salvage rate of 82% with rhTNF-alpha along with IFN gamma and melphalan. Edema, skin erythema and blistering were major postprocedural complications. Due to the expertise required only a few centres in Europe are currently using it.

Adjuvant Chemotherapy

Mainstay of treatment for STS remains surgery but radiation can be used in high grade marginally resected or recurrent tumors. Even with this approach, almost half of the cases invariably relapse and eventually die. This raised the question whether adjuvant chemotherapy could help in improving the survival. Several trials have been done in this regard and for a better understanding, all adjuvant trial can be arbitrarily divided into two generations based on chemotherapy agent used. Earlier trials before 90's, incorporated anthracycline (doxorubicin) mostly alone while the second generation trials used combination of anthracycline with ifosfamide. Prior to 1990s, 14 published randomized trials were done comparing surgery alone versus surgery plus doxorubicin as an adjuvant chemotherapy [9]. The results were conflicting with only two trials demonstrating survival benefit. In 1997, sarcoma metaanalysis collaboration (SMAC) analysis of 14 studies including 1,568 patients with a median follow up of 9.4 years was deemed the most reliable [10]. This landmark publication comparing doxorubicin as adjuvant versus no chemotherapy provided the evidence that chemotherapy significantly improved the time of local recurrence and distant metastases in addition to recurrence free survival. These was a trend towards improvement in overall survival with a survival advantage of 4% (p value insignificant). In a subset analysis of extremity sarcomas, 7% benefit was seen ($p=0.029$). The second generation of adjuvant trials with ifosfamide in combination with hematopoetic growth factors differed from the earlier trials in recruiting mostly extremity and high grade sarcoma cases. Here four trials are worth mention, two were positive trials and other two were negative trials. First was an Italian trial, that compared no postoperative therapy to five cycles of adjuvant chemotherapy with dose intensive ifosfamide/epirubicin combination and growth factor. This demonstrated a significant difference in 5 years overall survival for chemotherapy arm (66 vs 46%) ($p=0.04$) [11]. It received some criticism due to recruitment of high grade, extremity sarcomas and chemosensitive histologies. A second Italian trial also demonstrated a 5 year statistically significant survival benefit (72% vs 47%) in favour of chemotherapy arm. Chemotherapy used here was epirubicin with or without ifosfamide [12]. In contrast the other two negative trials EORTC and an Australian trial failed to demonstrated any benefit whatsoever. Kattan and colleagues have developed a post operative nomogram that combines variables including age at diagnosis, tumor size (≤5, 5 to 10, or >10 cm), histologic grade (high or low), histologic subtype and site to predict the probability of 12-year sarcoma-specific death using a database of 2,136 prospectively followed adult patients who were treated at a single institution [13].

A recent updated metaanalysis in 2008 that includes 1,953 patients recruited in 18 randomized trials favoured chemotherapy arm in terms of odd ratio for local recurrence 0.73 (95% CI :0.56–0.94) and distant/overall recurrence 0.67 (95% CI :0.56–0.82). In contrast to single agent doxorubicin, combination of doxorubicin and ifosfamide was found to improve over survival with statistical significance.

All the published data till date relates to extremity sarcomas and extrapolation of this data to other histological types seems to be inappropriate. To conclude ifosfamide in combination with doxorubicin remains the standard of care for completely resected sarcomas with high risk features (deep location, size >5 cm, high grade). In terms of overall survival benefit the data remains equivocal. In case of recurrent disease chemotherapy may be tried where local treatment is difficult. There is limited data on the role of chemotherapy in management of GISTs, retroperitoneal sarcomas (well differentiated), clear cell sarcomas, malignant solitary fibrous tumors, chordomas and with the available evidence they seem to be relatively chemoresistant. Imatinib mesylate particularly has shown impressive results in treatment of GISTs and is approved for adjuvant and metastatic cases.

Chemosensitive Sarcomas

Synovial Sarcoma

It accounts for 5–10% of sarcomas and seems to be the most chemosensitive tumor with good response to ifosfamide in combination with doxorubicin [14]. A possible exception is myxoid/round cell liposarcoma that is particularly more sensitive to ifosfamide.

Leiomyosarcoma

Data is conflicting regarding the role of docetaxel and gemcitabine as a single agent. Their combination seems to be rather more effective. Hensley et al. first reported a clinical benefit with combination in patients of uterine leiomyosarcoma [15]. In first line settings, a 35% overall response rates was seen (5% CR), 26% had stable disease and median overall survival was more than 16 months [16]. As second line, response rates of

27% with complete response of 6% was seen. The median progression free survival was over 5.6 months and median duration of response was 9 months [17].

Angiosarcoma

They are rare set of aggressive neoplasms with poor outcome. Although taxanes have shown limited activity in treatment of soft tissue sarcomas, paclitaxel appears to have specific efficacy in angiosarcomas. Fata and colleagues reported activity of paclitaxel in face and scalp angiosarcomas with eight patients out of nine achieving either CR or PR [18]. Another agent liposomal doxorubicin appears to be a potent alternative agent particularly for skin angiosarcomas [19, 20].

Newer Drug: Trabectedin (Ecteinascidin-743, ET743)

It is a marine derived alkaloid, obtained from tunicate Ecteinascidia turbinate found in Caribbean seas. It acts by binding to minor groove of DNA, distorting DNA and inhibiting transcription. Trabectedin demonstrated a promising role in treatment of metastatic STS resistant to anthracyclines and ifosfamide. Antitumor activity has been reported against liposarcomas (myxoid/round cell), leiomyosarcoma and synovial sarcomas. The recommended dose is 1.5 g/m2 over 24 h as a continous infusion (central line) once every 3 weeks. Disease stabilization was seen in up to 60% for synovial sarcomas and leiomyosarcomas [21, 22]. Promising results were also seen in myxoid/round cell liposarcoma in a retrospective study. Major side effects are neutropenia, thrombocytopenia (50% & 20% respectively) and mild transaminitis in 35–50% cases.

Future Trends

M-tor Inhibitors

'mTOR' is a cytoplasmic serine/threonine protein kinase involved in key cell cycle signaling. Growth factor like insulin (IGF) primarily regulates the mTOR pathway signaling through the PI3K/Akt pathway. Inhibition of mTOR affects the downstream messengers and renders the cell in G1 arrest. Rapamycins synthetic analogs, CCI-779 (temsirolimus), RAD001 (everolimus), and AP23573 (deforolimus) have been developed. Interim results of a phase II trial of deforolimus in patients with advanced soft tissue and bone sarcoma are encouraging with 24% patients experiencing a clinical response (defined as complete or partial response or stable disease for at least 16 weeks using RECIST), but the objective response rate was as low as 2.6%. Ridaforolimus in a Phase III study "SUCCEED trial" in the metastatic soft tissue sarcoma, (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) at a dose of 40 mg/day, 5 of 7 days per week demonstrated an improved progression-free survival (PFS) compared to placebo. Oral ridaforolimus was granted a Special Protocol Assessment (SPA) by the FDA for the SUCCEED trial. Main toxicities of Mtor inhibitors are mucositis, skin rash, and elevated hepatic transaminase.

Insulin like Growth Factor-1 Inhibitors

IGF system is composed of three ligands (IGF-1, IGF-II, and insulin), four receptors, and at least six high affinity binding proteins and binding proteases, of these IGF 1 being the most important. Activated IGF-1R recruits and phosphorylates adaptor proteins which leads to the activation of PI3K and MAPK pathways. The IGF-1R is the most commonly activated pathway in a variety of sarcomas like synovial, rhabdomyosarcoma, liposarcoma, leiomyosarcoma and ewings sarcoma. The two most common strategies to block IGF-IR are the use of monoclonal antibodies (mAbs) and small kinase inhibitors still undergoing trials. The main toxicities can be hyperglycemia and CNS toxicity.

Antiangiogenesis Agents

Angiogenesis plays an important role in the growth and dissemination of STSs. High VEGF expression is an independent poor prognostic factor for increased risk of metastases and decreased overall survival. The expression of VEGF, PDGF-b (Platelet derived growth factor-beta), MMP-2, MMP-9 (matrix metalloproteinase), and uPA (uroplasminogen activator) is associated with high tumor grade and usually with short metastasis-free survival. This may be due to VEGF-induced increased expression of bcl-2 and antiapoptotic factors. Monoclonal antibodies like bevacizumab and tyrosine kinase inhibitors (TKIs), sorafenib, sunitinib, and pazopanib are undergoing trials in this regard.

Summary

Soft tissue sarcomas represent a heterogenous group of neoplasms with differential sensitivity to chemotherapy. Their optimal management requires a multidisciplinary team approach. In the present era, the role of neoadjuvant chemotherapy is still controversial, adjuvant trials have shown survival benefit in certain situations but the results are not unanimous, In metastatic settings, choice of single agent or combination of drugs should be individualized and discussed with family members for better palliation. With the intensive research in this field, a better understanding of molecular pathways and the arrival of targeted therapies on the scene the future looks quite promising.

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Conflicts of interest None

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