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Introduction

Soft tissue sarcomas are a very complex group of rare mesenchymal tumors, including more than 50 different entities [1]. Local relapse (10-30% of cases) and metastatic diffusion (40% of cases) are two main issues in the control of the disease. In limited pulmonary metastasis, surgical metastasectomy is the treatment of choice. When not surgically manageable, metastatic disease is treated with medical treatment. Unfortunately, the overall survival is poor (12-15 months). In order to improve this dismal result, three main fields of research have been explored [2,3]:

- Reducing local relapse and metastatic spreading with adjuvant or neoadjuvant chemotherapy
- The introduction of more lines of treatment
- The discovery of new drugs (either chemotherapy or targeted agents)

Adjuvant and neoadjuvant CT

Adjuvant systemic chemotherapy has been studied in order to reduce both local and distant relapse of disease. Some randomized clinical trials and two meta-analyses were conducted in order to address this problem. Most studies used anthracyclines (adriamycin or analogues) +/- ifosfamide in the adjuvant setting. Unfortunately, the benefit both in survival and relapse was unsatisfying with a percentage of 5 and 10% of distant and local control respectively. As a consequence, adjuvant CT is not a standard treatment in STS and can be offered to some patients only, after an informed and shared decision-making. Adjuvant CT is currently offered to young patients in good performance status who underwent a surgical resection of high grade, deep and large (> 5 cm) STS [5-8].

Several randomized controlled trials on adjuvant CT have been conducted and published since the 1970s. Adjuvant trials can be divided in two main areas:

a. First generation CT with anthracyclines alone or in various combinations [4,5]

b. Second generation trials with anthracyclines + ifosfamide and GCSF support [6,7,8].

The first generation studies were grouped in a famous meta-analysis [5] which demonstrated a survival benefit of 10% and a local relapse of 5%.

Abstract

Soft tissue sarcomas (STS) are a group of different diseases that differ in presentation, response to therapies and prognosis. Some new interesting approaches are becoming available in the treatment of locally advanced as well as metastatic disease, leading to an improvement of patient’s survival. Neoadjuvant chemotherapy has the aim to limit the extension of surgery and to improve the systemic control of the disease and it is currently widely accepted. In the metastatic setting the modern concept of histology-driven therapy has overcome the universal use of the combination of Antracyclines and Ifosfamide in all subtypes of STS.

Some recent chemotherapeutic agents such as Trabectidine, Eribuline, or targeted compounds such as Pazopanib, Imatinib, Crizotinib, and Sunitinib have a defined role in some specific STS. Olaratumab, an anti PDGFRα monoclonal antibody, has recently been approved in combination with Doxorubicin as first line treatment in metastatic STS. Second line treatment is now adopted in many patients and leads to PFS and TTP improvement. Now-a-days the role of supportive care to increase the activity and to reduce toxicity of chemotherapy is well recognized.

Conversely, despite biological evidence supporting the role of immunotherapy in STS, adoptive and anti check point inhibitors therapies failed to show any activity and different further approaches are awaited.
The second generation studies had some common characteristics: higher doses of CT agents, GCSF support, volume of disease > 5 cm, high grade histology, various combination with radiotherapy [6,7,8].

The second meta-analysis published in 2008 confirmed the small benefit of the previous Antmann’s study and added a statistical significant benefit in overall survival for adriamycin + ifosfamide (p 0.01) [7].

The main limitation of the two meta-analyses is that they conflict with the singles studies considered; as the benefit of adjuvant chemotherapy can be detected only in large number of cases.

Hence, there is no consensus on the current role of adjuvant chemotherapy, and postoperative therapy is not a standard in adult STS. It is suggested as an option in high grade, deep, > 5 cm STS, after a shared final decision with the patient [2].

Over the last years the neoadjuvant approach has had an increasing role, given the several advantages over adjuvant therapy. Neoadjuvant chemotherapy can increase the rate of conservative surgery, reducing the need of amputations. At the same time neoadjuvant therapy can improve survival by destroying micro metastatic deposits. Preoperative CT can also give important information about chemo sensitivity of sarcoma on pathological samples. Lastly, CT administered preoperatively has a lower level of toxicity and it is administered on patients with a better Performance Status [2,10,11].

Two recent Italian studies demonstrated the activity of neoadjuvant treatment. First, Gronchi et al. compared 3 cycles of epirubicin (120 mg/m²)+ ifosfamide(9 g/mq) given preoperatively with 5 cycles (3 pre and 2 post surgery) of the same scheme on STS of the trunk and extremities. No differences in survival were found in the two arms; however the study did not rule out the activity of the combinator in different histotypes of STS [11,12].

In fact STS are a complex group of tumors with different chemo sensitivity (leiomyosarcomas, liposarcomas, Malignant Peripheral Nerve Sheath Tumors (MPNST) and undifferentiated pleomorphic sarcomas are the most common subtypes, but rare and even exceptionally rare histotypes are also represented).

Some studies were conducted in the advanced disease to address the issue of histotype-tailored therapy. With such aim, in a multinational study the Italian and Spanish sarcoma group ISG-STS-1001 compared epirubicin (120 mg/m²) and ifosfamide (9 g/mq) for 3 cycles in a neoadjuvant setting with 3 cycles with histology-driven therapeutic regimens. In summary the different groups were as follows [12]:

- For undifferentiated pleomorphic sarcoma, gemcitabine 900 mg/m² on days 1 and 8 intravenously over 90 min plus docetaxel 75 mg/m² on day 8 intravenously over 1 h, repeated every 21 days
- For leiomyosarcoma, gemcitabine 1800 mg/m² on day 1 intravenously over 180 min plus dacarbazine 500 mg/m² on day 1 intravenously over 20 min, repeated every 14 days;
- For high-grade myxoid liposarcoma, trabectedin 1.3 mg/m² via 24-h continuous infusion, repeated every 21 days;
- For synovial sarcoma, high-dose ifosfamide 14 g/m², given over 14 days via an external infusion pump, every 28 days;
- For malignant peripheral nerve sheath tumour, intravenous etoposide 150 mg/m² per day (days 1, 2, and 3) plus intravenous ifosfamide 3 g/m² per day (days 1, 2, and 3), repeated every 21 days

In a median follow up of 12.3 months only trabectidin in myxoid and round cells liposarcoma was comparable to standard epirubicin + ifosfamide. All the other experimental arms were inferior to the control arm in terms of disease free survival (38% vs 62%) and overall survival (64 % vs 82%). Based on those results, the current standard of care in clinical practice is 3 cycles of epirubicin + ifosfamide at standard doses [12].

Chemotherapy can also be integrated with Radiation Therapy. Combined treatment can increase the local response but can worsen the local side effects and general toxicity (neutropenia, thrombocytopenia, local tissue damage) [13-15].

The combination of CT and RT was tested in the above mentioned Italian- Spanish study with epirubicin + ifosfamide and in the RTOG 9514 study which investigated MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) combined with preoperative split-course RT and three cycles of postoperative chemotherapy. The US study also showed a high degree of toxicity with a 5 year DFS of 64% and OS of 71% [12-16].

In conclusion, neoadjuvant CT alone can improve the local control and operability of extremities, girdles and trunk STS. No mature data are available on five-year OS and a longer follow up is needed [2,11,12].

Metastatic disease

About 50% of all adult STS is metastatic at first diagnosis or becomes stage IV in the following years. The treatment choice is complex and must be done as a multidisciplinary decision [1,2]. Limited and resecable lung metastasis without extra pulmonary involvement should be treated with surgery, whenever radical resection is feasible [2,17,18]. Chemotherapy after surgery is an option, but there is not an evidence-based data for a better outcome [2].

In all other cases of metastatic disease, frontline chemotherapy is the standard treatment. The main agents are anthracyclines alone or in combination [19-21].

Many studies in the 80’s and 90’s and the METASARC database on 2165 adult patients with STS treated by the French Sarcoma Group from 1990 to 2013 demonstrated that polichemotherapy gives a better response rate than anthracyclines alone [22] (Table 1).

All singles studies failed to demonstrate that polichemotherapy is superior to adriamycin single agent in terms of overall survival [19-21]. Conversely, the METASARC study showed improved survival of patients treated with combination therapy (p=0.003 HR 0.822) [22]. Currently polichemotherapy can be offered when tumor shrinkage is expected to provide clinical benefit, but with specific concern about higher toxicity. Combination Chemotherapy can be advised in young and good performance status patients [2].
Similar results were showed in the randomized clinical trial by Judson et al [20].

Moreover METASARC gives other important suggestions to be confirmed by direct future studies [22]. In the study conducted by Savina et al, patient with leiomyosarcoma had longer PFS and OS than those with different histology, whereas patients with unclassified pleomorphic sarcoma had a very poor prognosis.

As consequence, histology-driven therapy seems to be important in decision making [23].

Synovial sarcomas seem to respond better to high dose ifosfamide but the activity of this agent is limited in leimiosarcoma [24]. Taxanes have a low activity in most adult STS but they seem to increase response rate when used as single agents in angiosarcoma and in combination with gemcitabine in leimiosarcomathey seem to increase RR [25,26].

Trabectidin is a semisynthetic agent, from a marine derived anti neoplastic compound isolated from Ecteinascidia turbinata. The drug binds the minor groove of DNA, interfering with DNA transcription to RNA. Trabectidin demonstrated specific activity against L-type sarcomas (leimiosarcoma and liposarcoma) and showed a higher ORR and PFS as compared to the active control with dacarbazine [27-29].

Many authors agree that other histological subtypes of adult STS can be treated with different agents other than anthracyclines +/- ifosfamide, i.e. adipocytic tumors can be approached with eribulin, epithelioid sarcomas with gemcitabine and solitary fibrous tumours (SFT) with dacarbazine [22,30,31,32].

New Drugs

Aldoxorubicin is an anthracycline prodrug of Adriamycin with a pH sensitive linker that mediates the binding with plasma endogenous albumin. The complex albumin-aldoxorubicin has a specific target in the acidic tumor environment and adriamicin is released in the neoplastic cell. In a phase II randomised trial, 123 patients received doxorubicin or aldoxorubicin. The newer drug had superior efficacy in PFS (5.6 vs 2.7 months) and RR (25% vs 0%). An interesting activity was found in mixoid Liposarcoma [33].

Another new anthracycline is amrubicine, which demonstrated less toxicity compared to adriamycin as single agent in a series of 24 non pretreated STS. The observed RR and PFS (13% and 5.8% respectively) are comparable to the parental drug, yet with lower cardiotoxicity and no alopecia [34].

Unlike these positive results, palifosfamide (an active analogue of ifosfamide) failed to demonstrate any superior activity in the Picasso III study (PFS was 5.2 months vs 6 months) [35].

Targeted Therapies

The discovery and the development of new agents against specific cell targets has opened new hopes and fields of investigation in the last 15 years. Tyrosine kinase inhibitors are small molecules active against specific trans-membrane receptors (i.e. EGFR, c-Kit, PDGFR) as well as intracellular signalling mediators [36].

Imatinib, very active against GISTs, has demonstrated some activity also in DermatoFibroSarcoma Protuberans (DFSP). This low grade sarcoma is characterized by the COL1A1/PDGFBtranslocation, leading to a fusion gene responsible for overactivation of PDGFB. In case of inoperable disease or relapse, Imatinib can be considered as a possible first line option. The fibrosarcomatous variant of DFSP shows better but short lasting responses, compared to the classical form [37].

Pazopanib is a TKI molecule investigated in two different studies, the phase II and III PALETTE trials. Pazopanib targets the angiogenetic pathways: VEGFR1-3, PDGFRα, PDGFRβ and c-kit. The drug has demonstrated good activity in different types of STS such as leiomyosarcomas, sinovialsarcomas, haemangiosarcomas, solitary fibrous tumor, yet not in liposarcomas. The drug has been approved for second and further lines of therapy [38,39].

Regorafenib is a small molecule approved as third line treatment in CRC; it has shown a mild activity in non-adipocytic STS previously treated with an anthracycline in a single arm French study. The drug targets VEGFR1-3, PDGFRα, PDGFRβ and c-kit. It is currently not approved in STS by the regulatory agencies [40].

Cediranib, an ALK inhibitor, has shown good activity in ASPS (Alveolar Soft Part Sarcoma) a rare sarcoma resistant to conventional therapies and with metastatic brain tropism [41].

Among the new targeted therapies in STS, monoclonal antibodies could also have an interesting role. They act against the extracellular

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**Table 1:** Oldest studies confronting adriamycin single agent versus Adriamycin in combination.

<table>
<thead>
<tr>
<th>Authors</th>
<th>regimen</th>
<th>N pts</th>
<th>RR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenfeld</td>
<td>A/AVC/AdVC</td>
<td>200</td>
<td>A 27%</td>
<td>ns</td>
</tr>
<tr>
<td>Muss</td>
<td>A/AC</td>
<td>104</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Omura</td>
<td>A/AD</td>
<td>146</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Borden</td>
<td>A/AD</td>
<td>186</td>
<td>AD 30%</td>
<td>ns</td>
</tr>
<tr>
<td>Lerner</td>
<td>A/AD</td>
<td>66</td>
<td>AD 44%</td>
<td>(leiomyoS)</td>
</tr>
<tr>
<td>Santoro</td>
<td>A/AC/ACYVADIC</td>
<td>449</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Borden</td>
<td>A/AVd</td>
<td>295</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Edmonson</td>
<td>A/AI/APM</td>
<td>262</td>
<td>AI 34%</td>
<td>ns</td>
</tr>
<tr>
<td>Antman</td>
<td>AD/MAID</td>
<td>340</td>
<td>MAID 32%</td>
<td>n</td>
</tr>
</tbody>
</table>
domains of TKI receptors. The most recent and innovative study was conducted by Tab et al., exploring the activity of Olaratumab and doxorubicin versus doxorubicin alone as a first line treatment of metastatic STS. Olaratumab is a human MoAb active against PDGFRα, antagonizing the activity of PDGF-AA, PDGF-BB, and PDGF-CC ligands on the receptor. Olaratumab combined with doxorubicin led to a PFS of 6.6 months vs 4.1 months in the control arm with doxorubicin alone (ORR of 18.2% vs 11.9% and OS of 26.5 months vs 14.7 months). Due to the clear clinical benefit shown in this setting, Olaratumab has obtained an accelerated approval by Food and Drug Administration and European Medicines Agency. The important discrepancy between PFS and OS has requested a confirmatory study in order to determine the precise mechanism of action of the drug, its activity against specific histological subtypes as well as its long terms results. Two different studies are now completing the recruitment [42].

No other MoAb has yet shown any activity against adult STS. Bevacizumab has failed to demonstrate activity in angiosarcoma both as a single agent and in combination [43]. Negative results were also found with TKI molecules in the same setting, only Sorafenib showed some interesting activity in angiosarcoma or haemangiosarcoma [44].

Ridaforolimus, a mTOR inhibitor with a wide activity as a Serine/Threonine kinase, failed to obtain a stabilization of disease as a maintenance therapy in advanced STS, in the placebo-controlled phase III succeed trial [45,46]. Temsirolimus and sirolimus showed some activity in haemangiendothelioma but the initial results were not confirmed [47,48]. Sunitinib has demonstrated initial activity in lymphangioma and lymphangiosarcoma not confirmed in more mature trials [49,50].

Ipatinib is not active in other mesenchymal tumors except for GISTs and DFSP.

Negative results were found with anti-IGFR inhibitors Cixutumumab and figitumumab [51,52].

**Second Line Therapy**

The precise role of salvage therapy in adult STS has not been well established yet. However, second line therapy has been used in patients with good performance status since the 1990s. Bramwell and colleagues demonstrated a higher activity of ifosfamide vs cyclofosfamide (24% vs 5%) in this setting [53]. In Verweij’s study, doxorubicin was superior to docetaxel as second line treatment in no selected STS [54]. Comparing gemcitabine and docetaxel vs gemcitabine alone, Maki found a higher activity in the combination arm in terms of ORR, PFS and OS. The highest activity was seen in UPS (Undifferentiated Pleomorphic Sarcoma) and in leiomyosarcoma (uterine and non-uterine) [55]. Conversely, Pautier et al. did not confirm the superiority of the combination over gemcitabine as a single agent, hence this drug is now recommended in second line in leiomyosarcoma, UPS and angiosarcoma [56]. In the above mentioned study of Garcia del Muro et al., leiomyosarcoma and other histological types were found to be sensitive to the combination of gemcitabine and dacarbazine [31]. In second line treatment Demetri et al. published the superiority of trabectedin over dacarbazine in patients with advanced myxoid round cell liposarcoma and in leiomyosarcoma [57]. Eribulin is active in liposarcoma as well as fibrosarcoma, epithelioid sarcoma and SFT, as shown in a randomized study comparing eribuline to dacarbazine [30]. Pazopanib has demonstrated a good activity as second or further lines of treatment in leiomyosarcoma and synovial sarcoma, not in liposarcoma [39].

All these studies were RCT. However the results and the analysis on histological subtypes were biased by the extent of the accrual.

To the current date, no benefit has been shown for third or further lines of therapy.

**Localized Therapy for Metastatic Disease**

The METASARC analysis supports the observation that patients who underwent additional localized therapy for metastatic STS had a better prognosis than those treated with exclusive chemotheraphy [22].

Local therapies include surgical resection of limited disease, ablative therapies or radiotherapy. This is an innovative approach, since local treatment is rarely given in metastatic STS [58].

Leiomyosarcoma, synovial sarcoma and MPNST seem to be the subtypes more likely to respond to localized therapies [58].

**Immunotherapy**

Despite some biological evidence that supports the activity of immunotherapy in STS, available results are not encouraging. Few studies offer stable and reproducible results and objective responses are low (not more than 8%) and short lasting. Standard checkpoint inhibitors seem to be inactive in these tumors [59,60].

**Conclusions**

As shown in our review, new data is emerging in adult STS and the main key points can be summarized as follows:

i. Adequate surgery is the cornerstone treatment in this disease. The intervention must be performed in a high volume center.

ii. Adjuvant chemotherapy, despite a limited benefit both in RFS and OS, can be offered in high grade, deep, >5 cm STS of the extremities. Adjuvant chemotherapy is not a rescue treatment for inadequate surgery.

iii. Neoadjuvant chemotherapy +/- radiotherapy should be considered in high grade, deep and >5 cm STS in order to increase resectability and distant control of the disease. Three cycles are recommended. At present, this approach in local disease is the preferred one.

iv. In metastatic disease, combination therapy with adriamycin + Ifosfamide is the standard of care in good performance status patients. In patients with lower performance, single agent adriamycin is the drug of choice.

v. Whenever feasible, repeated surgery on lung secondary lesions improves survival in metastatic disease.

vi. Histology-driven therapy has a well established role in first as well in second line treatment. Unfortunately, specifically active drugs have not been found for all STS subtypes. Antracycline+Ifosfamide is the standard for all sarcomas (Table 2).
Table 2: Histology oriented therapy; Evidence from literature.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Chemotherapy</th>
<th>Thyrosine kinase drugs and other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>Gemcitabine, paclitaxel</td>
<td>Pazopanib, Sunitinib, Cediranib</td>
</tr>
<tr>
<td>Angiosarcoma/intimal sarcoma</td>
<td></td>
<td>Pazopanib, Sorafenib</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td></td>
<td>Pazopanib, Sunitinib</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>High-dose ifosfamide, trabectedin, eribulin</td>
<td>Imatinib, Sorafenib, Sunitinib</td>
</tr>
<tr>
<td>Dermatofibrosacomaprotubersans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid/Hemangiendothelioma</td>
<td>Pazopanib, m-TOR inhibitors, Interferon</td>
<td></td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>Gemcitabine</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>Extraskeletal myxoidchondrosarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumour</td>
<td>Gemcitabine</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Gemcitabine, Docetaxel, Trabectedin, Dacarbazine</td>
<td>Pazopanib</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>Trabectedin, Erubulin</td>
<td></td>
</tr>
<tr>
<td>Perivascularepithelioidcelltumor</td>
<td>Gemcitabine</td>
<td>m-TOR inhibitors</td>
</tr>
<tr>
<td>Solitary fibroutumor</td>
<td>Dacarbazine</td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Ifofamide, Trabectedin</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>High-dose ifosfamide, Gemcitabine</td>
<td>Pazopanib</td>
</tr>
</tbody>
</table>

*From literature not all drugs are approved by the National Regulatory Agencies

vii. Targeted therapies have a limited role. Two targeted agents have shown activity: Imatinib in DFSP and Pazopanib in non-adipocytic soft tissue tumors. Olaratumab combined with doxorubicin as first line therapy seems to be promising.

viii. Second line treatment has a well established role in good performance status patients. All other patients should be offered best supportive care.

ix. Immunotherapy has not yet a specific role in this setting.

In conclusion, adult STS remain a group of neoplasm's with a global dismal prognosis. Only 53% of the patients are alive at five years from diagnosis. Despite these results, new perspectives will be coming from pharmacological studies, genetic and epigenetic investigations.

References


