Introduction

Soft-tissue sarcomas (STS) are a group of rare but highly heterogeneous neoplasms with mesenchymal origin. The curative management for localized disease is surgical resection, combined with or without radiotherapy (RT) for selected patients. Systemic treatment with cytotoxic chemotherapy and molecular targeted agents is one of the main therapeutic modalities in patients with advanced or metastatic disease. While adjuvant and neoadjuvant chemotherapy for pediatric sarcoma such as rhabdomyosarcomas, Ewing sarcomas and osteosarcomas is established, its role in adult-type sarcomas remains controversial. With the increasing knowledge in the molecular basis of pathogenesis of sarcoma and emerging of novel drugs, the treatment outcomes for patients with STS will improve greatly in the future. In this review, we aim to summarize the advances of chemotherapy, targeted therapy and immunotherapy in the management of STS.
Adjuvant chemotherapy for STS

There is an urgent need to determine the role of adjuvant chemotherapy for STS since up to half of high-risk patients will eventually relapse or develop distant metastasis. Over 20 studies on adjuvant therapy for STS have been performed. Unfortunately, these trials reported conflicting data. Most of them have been small, enrolled different risk patients and treated with different chemotherapy regimens. Two meta-analyses conducted on the randomized controlled trials regarding adjuvant chemotherapy for STS by Sarcoma Meta-analysis Collaboration (SMAC) have further explored the potential benefit of adjuvant chemotherapy for resected STS in adults. The first meta-analysis was published in 1997 including 14 studies which involved 1,568 adults with postoperative STS (extremities and others) to receive or not receive adjuvant doxorubicin-containing chemotherapy (1). After a median follow-up of 9.4 years, it was demonstrated a significantly lower risk for relapse, either local or distant metastatic, in chemotherapy arm than in observation arm, but the overall survival (OS) was not statistically significant although there was a trend towards improved [hazard ratio (HR) for death 0.89, 95% confidence interval (CI): 0.76–1.03]. Five recent studies using ifosfamide as part of adjuvant therapy were added to the SMAC updated meta-analysis in 2008 (2). The odds ratios (OR) for local recurrence was 0.73 (95% CI: 0.56–0.94; P=0.02), for distant and overall recurrence was 0.67 (95% CI: 0.56–0.82; P=0.0001), all in favor of chemotherapy, consistent with those found in the earlier meta-analysis. In terms of survival, doxorubicin alone had an OR of 0.84 (95% CI: 0.68–1.03; P=0.09), which was not statistically significant. However, when doxorubicin combined with ifosfamide, it can translate into a gain in OS (OR 0.77, P=0.01) and absolute risk reduction of death of 6 %, which implies the role of ifosfamide in the adjuvant treatment of sarcomas.

The first large study to incorporate ifosfamide as part of adjuvant therapy for STS is from the Italian Sarcoma Study Group which was designed on relatively restricted enrollment criteria (3). A total of 104 high-risk postoperative patients (grade 3–4, primary diameter ≥5 cm or any size recurrent tumor) in extremities or girdles were randomized to the dose intensive chemotherapy group (5 cycles of epirubicin 60 mg/m² over 2 days and ifosfamide 1.8 g/m² over 5 days) or control group. After a median follow-up of 59 months, median disease-free survival (DFS) (48 vs. 16 months) and median OS (75 vs. 46 months) were significantly better in the chemotherapy arm. These data imply a survival advantage of high-dose intensified chemotherapy for patients with high-risk extremity STS.

Although there was a significant survival benefit for the trial of the Italian Sarcoma Group, no difference in the recurrence-free survival (RFS) or OS were demonstrated in the European Organization for Research and Treatment of Cancer (EORTC) trials. The largest phase III randomized study of adjuvant chemotherapy was EORTC-62931 (4). A total of 351 grade 2–3 completely resected patients were recruited to 5 cycles of doxorubicin 75 mg/m² and ifosfamide 5 g/m² per cycle versus observation. However, this study was negative which showed no statistically significant difference in terms of DFS or OS. The estimated 5-year RFS was 52% in both arms and OS was 69% (control arm) and 64% (chemotherapy arm), respectively. To explain the difference between Italian Sarcoma Study Group and EORTC 62931 is the latter study included a heterogeneous group of high and low risk patients (67% extremity tumors, 60% high-grade, 40% ≥10 cm) and its suboptimal dosage of ifosfamide. In another earlier large EORTC study, postoperative 486 patients were randomized to combination chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CyVADIC) for 8 cycles or observation (5). While DFS and local control were both better in the chemotherapy arm, OS was not significantly different between the two arms.

Even in the prospective randomized trials, the role of adjuvant chemotherapy cannot be defined if the population of patients is unselected. Most trials have involved relatively small patient population, with heterogenous groups of recurrence risk. The criteria used to select patients for adjuvant chemotherapy should be based upon who will truly benefit. How to define high-risk patients depends on several factors, including tumor grade, size, histological type, primary location and the quality of surgery. However, there is no universally accepted definition for high-risk patients in STS. The most widely accepted grading system is proposed by the Sarcoma Group of the French Federation of Cancer Centers (FNCLCC). Tumors are classified according to three parameters: the mitotic index, the presence of necrosis, and cell differentiation. This classification has demonstrated prognostic value, with 5-year survival rates of 95%, 75%, and 45% in patients with grade 1, 2, or 3 tumors, respectively (6).

A recent pooled analysis of the above mentioned two large EORTC studies aimed to evaluate whether adjuvant chemotherapy benefited any particular subgroup.
patients (7). However, RFS and OS were only improved in the R1 resection group. It failed to demonstrate any other factors (size, histology, grade) as predictors of improved survival on multivariate analysis.

Adjuvant chemotherapy has failed so far to consistently improve OS. The reason for that may be the criteria now used to select patients for adjuvant treatment (usually high grade, primary tumor ≥5 cm, deeply seated or locally recurrent extremity sarcomas) are not optimal. We need a clear risk stratification for patient selection for adjuvant therapy. Several prognostic nomograms have been developed to predict OS and risk of distant metastasis in patients undergoing resection of STS of the extremities, but all of them have some limitations (8,9). In the future, clinical design for adjuvant chemotherapy should incorporate these tools for accurate risk stratification.

Moreover, it should be recognized that chemosensitivity is another important factor for consideration in selection patients for adjuvant therapy. It is well known from studies in the metastatic sarcomas that myxoid/round cell liposarcomas and synovial sarcomas are relatively chemosensitive subtypes of STS.

To make some sense of who will be given adjuvant therapy, it is useful to bear in mind that it needs to be discussed on an individual case by case basis, taking into consideration site of disease (extremity/retroperitoneal/trunk), size, grade, histological subtypes, chemosensitivities as well as PS of the patient, comorbidities, and age. Recently, a mobile device called “Sarculator” which may predict 10-year probability of OS and incidence of distant metastasis in STS patients that can help us to identify high-risk STS patients who fit for adjuvant chemotherapy (10).

Neoadjuvant chemotherapy for STS

Neoadjuvant chemotherapy is already a well-adopted approach in the management of osteosarcoma. However, as the efficacy of chemotherapy for metastatic STS is relatively low, the role of neoadjuvant chemotherapy in adult STS is ill defined. There are many theoretical advantages for giving neoadjuvant chemotherapy before surgery, such as tumor cytoreduction for limb salvage surgery, elimination of micrometastases as well as prediction of the effectiveness of chemotherapy. However, in STS, there is lack of evidence specifically addressing the role of chemotherapy when used in a neoadjuvant setting. A European phase II trial enrolled 134 patients with resectable high-risk primary and recurrent STS (11). “High-risk” defined as tumors > or =8 cm of any grade, or grade II/III tumors <8 cm, or grade II/III locally recurrent tumors, or grade II/III tumors with inadequate surgery. These high-risk patients were randomized between either surgery alone or 3 cycles of doxorubicin 50 mg/m² and ifosfamide 5 g/m² before surgery. At a median follow-up of 7.3 years, the 5-year DFS is estimated at 52% for the no chemotherapy and 56% for the chemotherapy arm (P=0.3548). The 5-year OS for both arms is 64% and 65%, respectively (P=0.2204). Despite neoadjuvant chemotherapy with doxorubicin and ifosfamide at these doses and with this schedule was feasible and did not compromise subsequent treatment, it was not powered to draw definitive conclusions on benefit of neoadjuvant chemotherapy even in these selected high-risk patients. The low chemotherapy intensity used and patients with a large variety of histologies and varying chemosensitivities in this trial may potentially impact the possible benefit of neoadjuvant chemotherapy.

In light of the dose intense combination of ifosfamide (9 g/m²) plus epirubicin (120 mg/m²) with G-CSF support may improve therapeutic efficacy, a multicenter international phase III study (12) was designed by Italian Sarcoma Group and the Spanish Sarcoma Group (ISG) to compare 3 cycles of preoperative full-dose epirubicin and ifosfamide (arm A) with 5 cycles of the same drugs given perioperatively (3 neoadjuvant cycles followed by surgery and 2 further adjuvant cycles) (arm B). A total of 328 high-risk patients were recruited, with 164 patients in each arm. At a median follow-up of 63 months, 5-year OS probability was 0.70 for the entire group of patients (0.68 in arm A and 0.71 in arm B). The HR of arm A versus arm B was 1.00 (90% CI: 0.72–1.39). It was concluded from this study that 3 cycles of full-dose preoperative chemotherapy were not inferior to 5 cycles of perioperative chemotherapy in terms of survival. In 2016, Gronchi et al. reported on their 10-year long-term follow-up of this trial (13). The non-inferiority of 3 cycles in comparison to five is confirmed. These results showed that if 3 cycles of full-dose neoadjuvant chemotherapy have been given, it does not need to give further adjuvant cycles. However, this study did not address whether these 3 cycles of full-dose chemotherapy given preoperative is superior or equal to postoperative with long-term survival.

Despite doxorubicin and ifosfamide are the two most active drugs in STS, there is more emerging evidence of different sensitivity to treatment for different histological subtypes. Promising activity has been reported from varying histology-specific regimens in treatment of metastatic STS. In a recently published phase III trial by ISG-
STS-1001), 3 cycles of neoadjuvant histology-tailored chemotherapy were compared to standard chemotherapy with full dose epirubicin and ifosfamide (14). 287 high-risk patients with five different histological subtypes of STS were randomly assigned to standard chemotherapy or histology-tailored therapy (trabectedin for high-grade myxoid liposarcomas (MLPS) (n=64), high-dose ifosfamide alone for synovial sarcoma (n=70), etoposide plus ifosfamide for malignant peripheral nerve sheath tumors (n=27), gemcitabine plus dacarbazine for leiomyosarcoma (LMS) (n=28), and gemcitabine plus docetaxel for undifferentiated pleomorphic sarcoma (UPS) (n=97). The primary endpoint was DFS. With a median follow-up of 12.3 months, the projected DFS at 46 months was 62% in the standard chemotherapy group, better than 38% in the histotype-tailored chemotherapy group (HR for DFS was 2.0, 95% CI: 1.22–3.26; P=0.006) across various histological subtypes, with the exception of high-grade MLPS, in which DFS was similar between trabectedin and standard chemotherapy. The OS probability at 46 months was 0.89 and 0.64 (log rank, P=0.003) in the standard and in the tailored arm, respectively. An absolute benefit of nearly 20% on PFS translates into an advantage on OS. Although neoadjuvant histotype-tailored chemotherapy regimen did not show any advantage over the standard chemotherapy regimen, the benefit with the standard chemotherapy regimen further confirmed the value of neoadjuvant chemotherapy itself in patients with high-risk STS.

From ESMO guideline, for STS, there is no consensus on the current role of adjuvant chemotherapy (15). It can be proposed as an option to the high-risk patient (high-grade, deep, >5 cm tumor) for a shared decision-making with the patient or within clinical trials. Adjuvant chemotherapy is not used in histological subtypes known to be insensitive to chemotherapy. If the decision is made to use chemotherapy as upfront treatment, it may well be used preoperatively. From the study of ISG-STS-1001, a benefit may be gained when 3 cycles of full-dose anthracycline-ifosfamide regimen in selected high-risk STS of extremity/trunk wall.

Chemotherapy in metastatic STS

First-line chemotherapy

For the majority of patients with unresectable and metastatic disease, systemic therapy is administered with palliative intention. As in the adjuvant setting, anthracycline and ifosfamide remain the cornerstone for more than 30 years regardless of subtype. However, there are few studies directly assessed whether doxorubicin should be administered alone or in combination with ifosfamide. The randomized phase III EORTC 62012 trial was conducted, a total of 455 locally advanced or metastatic, grade 2 or 3 soft-tissue sarcoma patients were randomly assigned to receive either single-agent doxorubicin (75 mg/m³) or doxorubicin (75 mg/m³) with ifosfamide (10 g/m³ over 4 days) with growth factor support (16). Patients were treated every 3 weeks for a maximum of 6 cycles or until progression. At a median follow-up of 56 months, the difference of OS did not achieve statistical significance. Median OS was 14.3 months with the combination and 12.8 months with doxorubicin alone (HR =0.83; P=0.076). Median PFS, however, was 7.4 months with the combination and 4.6 months with doxorubicin alone, for a 26% reduction in risk that was statistically significant (HR =0.74; P=0.003). The objective response rate (RR) was 26.5% with the combination and 13.6% with doxorubicin. Despite colony-stimulating factor support, the most common grade 3 and 4 toxic effects were all more common in the combination than in the doxorubicin alone group: leucopenia (43% vs. 18%), neutropenia (42% vs. 37%), febrile neutropenia (46% vs. 13%), anemia (35% vs. 5%), and thrombocytopenia (33% vs. <1%). The lack of OS advantage but with more toxicities for combination regimen do not support its routine use in the setting of advanced incurable disease unless there is an immediate need to decrease tumor bulk, improve symptoms or translate into resection.

Until now, the standard first-line treatment for STS has been doxorubicin. Is there any choice to consider when selecting first-line treatment beyond doxorubicin?

According to phase II and retrospective studies, the combination of gemcitabine and docetaxel may be effective in treating STS. The GeDDiS trial was a phase III, randomized, multicenter study to compare the combination of gemcitabine and docetaxel with doxorubicin in patients with previously untreated advanced unresectable or metastatic STS (17). Patients were randomly assigned to the control arm (75 mg/m³ of doxorubicin) or the investigational arm (675 mg/m³ of gemcitabine on days 1 and 8 plus 75 mg/m² of docetaxel on day 8 every 21 days). A total of 257 patients were enrolled, the median follow-up was 19 months. The primary endpoint of 24-week PFS was identical between arms, 46% each. However, patients in the investigational arm had lower dose intensity (83.3% vs. 94.6% for doxorubicin), more dose delays (55.5% vs. 45.7% for doxorubicin), and more withdrawals
because of unacceptable toxicity (10.2% vs. 0.8% for doxorubicin). Moreover, no differences in efficacy were found between histology subtype groups, such as LMS or nonleiomyosarcoma. This result again confirmed that single agent doxorubicin should be the preferred first-line option, given greater tolerability and potentially favourable efficacy.

Although doxorubicin remains a backbone for sarcoma treatment, its RR is relatively low while with significant toxicities. As doses exceeding 75 mg/m², doxorubicin is associated with cardiotoxicities, myelosuppression and mucositis. Several types of anthracycline have been recently tested in first-line treatment to improve its efficacy in STS. Aldoxorubicin is a novel albumin-binding prodrug of doxorubicin which contains a carboxylic hydrazone and covalently binds to albumin in the blood until reaching into tumor tissue, where the acidic microenvironment breaks the covalent bond with albumin and release doxorubicin. This allows for greater doses (3.5–4 times of the standard doxorubicin dose) of doxorubicin to be administered while reducing its side effects. An international multicenter phase 2b randomized study has evaluated the efficacy and safety of aldoxorubicin vs. doxorubicin in patients with advanced STS (18). A total of 123 patients with histologically confirmed metastatic, locally advanced unresectable STS were randomized 2:1 to receive 350 mg/m² aldoxorubicin (260 mg/m² doxorubicin equivalents) intravenous (IV) or 75 mg/m² doxorubicin every 3 weeks for up to 6 cycles. In this study, aldoxorubicin was associated with more than a doubling of both overall RR (ORR: 25% vs. 0%) and PFS (5.6 vs. 2.7 months; P=0.02). A similar percentage of neutropenic fever between two arms (15% vs. 16%), and a higher rate of decreased cardiac output was observed in doxorubicin arm (22%) compared with aldoxorubicin arm (11%). No patient treated with aldoxorubicin had ejection fractions below 50% versus 9.4% of patients that had received doxorubicin. Most importantly, there was no clinically significant reduction in cardiac function in the aldoxorubicin patients despite receiving high equivalent of doxorubicin dose. Aldoxorubicin represents a promising drug for treatment of sarcomas. The drug has minimal cardiac toxicity, which represents a significant advantage to doxorubicin. Preliminary phase 3 study results demonstrate PFS advantage in patients with LMS and liposarcoma. However, more studies are needed to establish the role of aldoxorubicin in sarcoma treatment.

Amlubricin is a third-generation anthracycline, which has been suggested to be less toxic than doxorubicin, especially for cardiac toxicity. A phase II multicenter single arm study was done to evaluate the efficacy and tolerability of amrubcin in advanced STS (19). A total of 24 patients were treated with amrubcin 40 mg/m² for 3 days in 21 days cycles in first-line therapy. The best ORR was 13%, median PFS was 5.8 months, and median OS was 26 months. Grade 3 to 4 toxicities of febrile neutropenia and anemia occurred in 21% of treated patients. There was no significant cardiac toxicity up to a cumulative dose of 4,800 mg/m². One patient with metastatic MLPS with TLS-CHOP translocation had a durable response thus indicate further study is warranted in this subtype.

Similar to aldoxorubicin and amrubcin, newer fosfamides, namely evofosfamide and palifosfamide have not yet led to substantial progress. Two randomised phase III clinical trials named SARC021 (20) and PICASSO (21) have tested doxorubicin in combination with evofosfamide or palifosfamide, respectively. In these two studies, the combination arm produced higher RR but more toxicity. Moreover, same as EORTC 62012 trial, there were no OS or PFS in favour of the combination arm.

Until now, doxorubicin with or without ifosfamide remains the standard first-line chemotherapy for most of STS.

**Histology-based second-line chemotherapy**

There is no standard regimen in second line treatment for STS. Beside anthracyclines and ifosfamide, there are other drugs with moderate activity in this disease. As different subtypes may have different sensitivity to different cytotoxic agents, beyond the first line, the treatment for STS is being increasingly driven by histology. For example, there is evidence of efficacy of gemcitabine in LMS and angiosarcoma; dacarbazine in LMS and solitary fibrous tumors (SFT); trabectedin in LMS and liposarcomas, especially in MLPS; taxanes and gemcitabine in angiosarcoma, eribulin in liposarcoma, etc.

**Eribulin**

Eribulin mesylate is an antimitotic agent, which acts by inhibiting microtubules’ growth. A phase 2 trial assessed the safety and efficacy of eribulin in pretreated STS 128 patients who received eribulin 1.4 mg/m² over 2–5 min at days 1 and 8 for every 3 weeks. The subtypes including adipocytic sarcoma (37 patients), LMS (40 patients), synovial sarcoma (19 patients), and other sarcomas (32 patients). The result was positive for primary goal (3-month PFS), in the group of adipocytic sarcoma with 46.9% patients were progression...
free at 12 weeks, and LMS [3-month progression-free rate (PFR): 31.6%] (22). Another randomized phase 3 trial in 452 advanced pretreated adipocytic sarcoma and LMS patients, 50% of patients received eribulin (1.4 mg/m², intravenous on days 1 and 8), the left over received dacarbazine (850–1,200 mg/m², IV on day 1) for every 21 days (23). The median OS for eribulin and dacarbazine was 13.5 and 11.5 months, respectively (HR =0.768, 95% CI: 0.618–0.954; P=0.017). The OS was significantly improved (15.6 vs. 8.4 months) in liposarcoma cohorts, while no sense was seen in LMS. Based on these results, the FDA approved the using of eribulin in advanced pretreated liposarcoma in 2016 (http://www.fda.gov/fda.gov). The most common grade 3–4 adverse events were neutropenia, anemia, fatigue, and febrile neutropenia.

**Trabectedin**

Trabectedin, derived from the marine ascidian, Ecteinascidia turbinata, is a natural alkaloid with multiple complex mechanisms of effects. Trabectedin, mainly binds to the minor groove of DNA and binds to guanine in N2 position, different from traditional alkylating agents which binds to the major groove of DNA and predominantly form crosslink to guanine in the N7 or O6 position (24). Trabectedin disturbs tumor cell cycle progression by retarding S-phase progression and inducing G2/M arrest (25).

In 2001, Delaloge et al. first reported the activity of trabectedin in 29 advanced STS patients who had failed in prior doxorubicin-based chemotherapy (26). In this investigation, there were 34.5% (10/29) stable disease (SD) sustaining more than 2 months and median time to progression of 2.8 months, 13.8% (4/29) PR, 6.9% (2/29) minor responses with shrinking at least 30% in size. A late study recommended the dosage of trabectedin to be 1.5 mg/m² as 24-H continuous intravenous infusion (CIV) once every 3 weeks (27). Morgan et al. (28) compared 580 µg/m² per week schedule with the “standard” 1.5 mg/m² 24-H CIV every 3 weeks schedule, the results indicated that every 3 weeks schedule superior to per week in median PFS (3.3 vs. 2.3 months; P=0.0418).

Several phase 2 clinical trials have been conducted to verify the efficacy of trabectedin alone or combine with other chemotherapy drugs in advanced STS patients who fielded in previous first-line chemotherapy (29-32). In a retrospective study (31), 885 advanced STS patients received the “standard” q3 weeks regime, and 227 of them continued trabectedin up to disease progression. The longer trabectedin treatment until disease progression is associated with a significantly improved PFS (11.7 vs. 4.4 months) and OS (24.9 vs. 12.2 months). In an expanded access program for 1,895 advanced STS following failure of prior chemotherapy, suggested the patients with LMS and liposarcoma had significantly longer OS (16.2 vs. 8.4 months, respectively) compared to all other histological subtypes, as well as higher RR (6.9% vs. 4%, respectively). Several trials tried to verified the efficacy of trabectedin in specific STS subtypes, mainly concentrated on LMS and MLPS (33-36).

In 2015, Demetri et al. launched critical randomized phase 3 study using trabectedin (n=345) vs. dacarbazine (n=173) in locally advanced, unresectable or metastatic LMS and liposarcoma (37). In the trabectedin arm, trabectedin (1.5 mg/m²) was administered as a 24-H CIV on day 1 of every 3 weeks, whereas in the dacarbazine arm, dacarbazine (1 g/m²) was administered by intravenous infusion over 20–120 min on day 1 of every 21-day cycle. OS was the primary end-point, and PFS was a secondary end-point. Fortunately, treatment with trabectedin resulted in a statistically significant improvement in PFS, with a PFS of 4.2 months and 1.5 months for trabectedin and dacarbazine, respectively (HR =0.55; 95% CI: 0.44–0.70; P<0.001). However, the primary end-point, interim analysis indicated no improvement in OS (HR =0.87; P=0.37). Based on these dates, the United States Food and Drug Administration (FDA) approved the trabectedin for the treatment of unresectable or metastatic liposarcoma or LMS that has failed a prior anthracycline-containing regimen.

MLPS is, characteristically associated with t(12;16) FUS-CHOP translocation which accounting for 90% variants of MLPS, a STS subtype which is particularly sensitive to trabectedin. The chimeric product of this translocation modulates the activity of the C/EBP pathway, which is implicated in G1-S phase cell cycle progression, growth arrest, apoptosis, and developmental programs (38). Some of transcription play a crucial role in adipocytic differentiation, the trabectedin may interfere with the activity of modulation and induce expression or accumulation of some proteins which associated with terminal adipocytic differentiation. While in Europe, the drug is approved for all STS, and it brought the experiences in treatment of other subtypes of STS. In a retrospect study of the using trabectedin in 61 patients with synovial sarcoma, 9 of them had a partial response (PR), and 21 of them had SD (39).

Although trabectedin brings new hope for specific subtypes of STS, the side effects also have to be taken...
into consideration. In previous investigation (37), the most common adverse reactions are nausea (75%), fatigue (69%), vomiting (46%), constipation and decreased appetite (37%), diarrhea (33%). Less common adverse reactions were dyspnea and headache (25%), arthralgia and insomnia (15%), and myalgia (12%). The grade 3–4 side effects were, less than 10%, neutropenia, thrombocytopenia, anemia, elevated liver enzymes. Thus, an important method in reducing toxicity is the use of dexamethasone prophylaxis 4 mg po BID the day before the trabectedin CIV, and markedly decreased the grade 3–4 advanced effects (P=0.0001) (40,41). At the same time, don’t forget to follow up blood biochemistry during trabectedin infusion.

With the efficacy of trabectedin and doxorubicin has firmly established in advanced STS, does the two drugs powerful combination will bring new hope for metastatic STS? In 2001, Takahashi and colleagues reported that the combination appeared to result in synergistic cytotoxicity in a sarcoma cell line. The trabectedin 24-H CIV prior to doxorubicin seemed to enhance the cytotoxic activity of the combination (42). Blay et al. studied a 60-mg dose of doxorubicin administered as a bolus with subsequent 3-H CIV of trabectedin. The results indicated that 83% of patients had SD, 12% of them had PR, but all patients presented dosing limiting neutropenia, and all need hematopoietic growth factor support, and the maximum tolerated dose was doxorubicin 60 mg/m² with trabectedin 1.1 mg/m² (43). Another nonrandomized phase II study of the combination of trabectedin and doxorubicin in soft tissue and uterine LMS adopted the dosing the same with Blay et al. 59.6% patients with PR and 27.7% with PR in the uterine LMS cohort, while 36.1% patients with PR and 52.6% having SD in the soft-tissue LMS cohort. The median PFS (8.2 vs. 12.9 months) and median OS (20.2 vs. 35.5 months) for uterine LMS and soft-tissue LMS respectively. Although lacking the date about the outcomes of patients with soft-tissue LMS, the authors still pointed out that the RR, PFS and OS in the uterine LMS cohort did compare favorably to other uterine LMS cohorts treated with combinations like gemcitabine and docetaxel or doxorubicin and ifosfamide (44-46). In a randomized phase II study compared the doxorubicin 75 mg/m² single agents with the combination of doxorubicin 60 mg/m² and trabectedin 1.1 mg/m² in a broader range of STS. Frustratedly, the study was stopped early because of the worsening expected PFS in experimental arm (47). The PFS in experimental arm and the control group was 5.5 vs. 5.8 months respectively. The second endpoints, RR and OS, were also no sense.

Above all, trabectedin is one of effective alternative chemotherapeutic drugs for unresectable or metastatic STS, especially in liposarcoma or LMS. If trabectedin is used in combination with other agents, special attention should be paid to the toxic reaction and the dosage of the drug, and at the same time take appropriately methods to reduce and monitor the toxicity.

Others

Both temozolomide and dacarbazine (DTIC), are alkylating agents, with temozolomide being a prodrug of dacarbazine which interferes with the biosynthesis of purine, showed activity in monotherapy in pretreated STS (48). In a prolonged schedule of temozolomide (75–100 mg/m² per day during 6 consecutive weeks) in 48 pretreated STS patients, the 3-month PFR was 39.5% and RECIST RR was 15.5%, and the efficacy lasting for a long time (median of 12.5 months) in responding patients (49). Another study indicated modest activity in pretreated STS, and the LMS group had a median PFS and OS of 3.9 and 30.8 months, respectively (50). These drugs could be especially interesting in LMS. What’s more, SFT also seems to benefit from dacarbazine and temozolomide based regimens (51,52)

The combination of dacarbazine and doxorubicin is one of the oldest drugs to have shown efficacy in STS. Primarily, DTIC was used as a monotherapy in advanced STS, and had a RR of 18%; but a short time to progression (53). A study compared doxorubicin alone with the combination of doxorubicin and DTIC, showed increase in RR in advanced STS (54). In 2013, a systematic review investigated the using of DTIC as second line therapy with and without gemcitabine (55). The results indicated the combination had a high rate of disease free progression at 3 months (54.2% vs. 35.2%, respectively).

Paclitaxel has widely used in tumor chemotherapy and also shown activity in STS. In a phase 2 trial conducted by French sarcoma group, 30 advanced angiosarcoma patients were treated with weekly paclitaxel 80 mg/m² days 1, 8, and the results showed that the 4-month PFS reached 45%. The same group also launched a combination trial of bevacizumab and paclitaxel, but failed to show the superiority to weekly paclitaxel (56). Another clinical trial also showed the activity in Kaposi sarcoma (57).

Thus, when we carry out chemotherapy regiments for STS, we’d better take the subtype, location, histological
grade, tumor size, surgical margin, tumor metastasis, and previous treatment into consideration. In addition, patient's factors should not be ignored, factors including, but not limited to, patients' willingness, physical status, potential toxic risks related to the treatment, as well as possible quality-of-life impairments. Therefore, a multi-disciplinary team discussion is essential for all advanced STS in order to propose appropriate strategies and maximize the therapeutic effects.

**Targeted therapy**

Because of the heterogeneity of STS and the lack of driver mutations, the development of targeted therapy is lagging. However, the investigations of sarcoma genomics and mutations of signaling pathway have revealed several candidates for targeted therapy, and the angiogenetic pathway was found to be one of the promising targets (58).

**Tyrosine kinase inhibitors (TKIs) targeting angiogenesis**

Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase (RTK) inhibitor that blocks tumour growth and inhibits angiogenesis. In the phase II EORTC 62043 study, patients were enrolled in four cohorts: LMS, liposarcoma, synovial sarcoma, and other histologies (59). The primary end-point was the PFR at 12 weeks, and the outcomes were evaluated in each cohort; 18 of 41 (44%) patients in LMS cohort, 18 of 37 (49%) patients in synovial sarcoma cohort, 16 of 41 (39%) patients in other histologies cohort reached the progression-free at 12 weeks. However, liposarcoma cohort was stopped because of only 5 of 19 (26%) patients reached the progression-free at 12 weeks. As a result, liposarcoma was excluded from the phase III study (PALETTE), in which median PFS was 4.6 months in the pazopanib-treated patients compared to 1.47 months in the control arm, the difference was very significant and the risk of disease progression was reduced by 67%. Moreover, ORR was 10.13% versus 1.33%, DCR was 55.7% versus 22.67%, respectively.

Other small molecular TKI targeting angiogenesis including sunitinib, sorafenib, regorafenib, cediranib and apatinib have shown moderate activity in LMS, synovial sarcoma, alveolar soft part sarcomas, solitary fibrous tumours and angiosarcomas in small sample, phase II trials. The selection should be based on histologic subtype, patient characteristics, toxicity profile and accessibility of the drug.

**CDK4/CDK6 inhibitor**

CDK4 has been regarded as another promising target in the treatment of STS. Overexpression of the protein in more than 90% of well-differentiated/dedifferentiated liposarcoma (WDL/DLS) has been found (64). Palbociclib is a CDK4/CDK6-inhibitor, in a phase 2 study, it was shown that a 12-week PFS rate of 66% in CDK4-positive WDL/DLS (65). The previous phase 2 study has already proved the favorable of PFS at the 200-mg dose (for 14 days, every 3 weeks). Another study of palbociclib in 60 advanced WDL/DLS (125 mg daily for 21 days in 28-day cycles), the results show that the 12-week PFS was 57.2 and median PFS was 17.9 weeks (66).

**Other TKIs**

With regard to other TKIs, imatinib is effective in dermatofibrosarcoma, mammalian target of rapamycin (mTOR) inhibitors are active in a proportion of PEComas (perivascular epithelioid cell tumours) and crizotinib in ALK-rearranged inflammatory myofibroblastic tumours.

**Monoclonal antibodies: olaratumab**

A possible breakthrough in the treatment of STS is represented by the recently published results of an open-label phase Ib/II trial comparing olaratumab and doxorubicin versus doxorubicin alone for first-line treatment of STS patients (67). Olaratumab is a recombinant monoclonal antibody that targets PDGFRα, blocking PDGF-AA, PDGF-BB and PDGF-CC. Previous studies had revealed that olaratumab might exert anti-
tumour activity in human sarcoma xenograft models (68). The results of the phase Ib/II study, randomising 133 patients to receive olaratumab plus doxorubicin or doxorubicin alone, showed a median PFS of 6.6 months (95% CI: 4.1–8.3 months) and 4.1 months (95% CI: 2.8–5.4 months), and an objective RR of 18.2% (95% CI: 9.8–29.6%) and 11.9% (95% CI: 5.3–22.2%), respectively.

The addition of olaratumab to doxorubicin indicated a much more improvement in OS, with a 11.8-month difference between these two arms. The median OS was 26.5 months (95% CI: 20.9–31.7 months) and 14.7 months (95% CI: 9.2–17.1 months) respectively. Based upon the improvement of OS, both FDA and EMA approved its use in the first-line setting in combination with doxorubicin. Until now, a confirmatory phase 3 study, the ANNOUNCE (NCT02451943), has finished enrollment.

**Immunotherapy: immune checkpoint inhibitors**

Immunotherapy has been one of the major breakthroughs in oncology. As for STS, the efficacy remains controversial. Of all the pathway discovered, PD-1/PD-L1 axis seems to attract the most attentions. Tumour PD-L1 expression has been reported in up to 65% of different subtypes of sarcomas and the degree of PD-1 positivity in tumour-infiltrating lymphocytes (TILs) and PD-L1 expression in tumor specimens from 105 cases of STS, has been correlated with a poorer prognosis and more aggressive disease (69,70). Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody which has been found that it could exert an antitumor effect in metastatic sarcomas (71). In a retrospective study, a total of 28 patients with a metastatic or unresectable soft tissue or bone sarcoma received nivolumab 3 mg/kg IV every 2 weeks alone (N=10) or in combination with pazopanib (N=18). Among 24 evaluable patients, 12 patients had clinical benefit (PR + SD), 12 had progressive disease (PD). They observed three PR: one dedifferentiated chondrosarcoma, one epithelioid sarcoma and one maxillary osteosarcoma (last two patients on pazopanib); nine patients had SD including three LMS; 12 patients had progression of disease including 4 LMS (71).

Pembrolizumab as a single agent showed activity in unselected sarcoma subtypes with an ORR of 17.5% and a 55% 3-month PFS; UPS and DDLS were the histologies that seemed to benefit the most. Compared with SARC028 study, another investigation enrolled 57 advanced STS patients [15 LMS, 16 UPS, 10 gastrointestinal stromal tumors (GIST) and 16 others] who received 50 mg twice daily cyclophosphamide 1 week on and 1 week off and 200 mg of IV pembrolizumab every 3 weeks (74). The exploration indicated that 31 patients (10, LMS; 7, UPS; 8, others; and 6, GIST) with PD and 16 patients (3, LMS; 5, UPS; 5, others; and 3, GIST) with SD, 3 patients (1 patient with a STF, 1 with an endometrial stromal sarcoma, and 1 with a GIST) with progression free for 6 months. One objective response was observed in a patient with initially progressive SFT. The 6-months non-progression rate was 0%, 0%, 14.3% and 11.1% for LMS, UPS, other and GIST, respectively. Further study found
that the unique PR patient with SFT bearing more than 10% PD-L1-positive immune cells and the tumor had mild IDO-1 (indoleamine 2,3-dioxygenase 1) positive immune cells, a lower CD68 positive cell density and a higher CD8-positive cell density. These findings may help us to further explore the mechanism of checkpoint inhibitors in STS.

The value of immunotherapy in STS is still largely unexplored. Further research focus on better patient selection and to investigate new combinatorial strategies.

**Summary**

Due to the advances of systemic treatment for STS in recent years, the outcome of STS has been greatly improved. As the molecular pathogenic basis of various histologic subtypes of STS has been revealed, the development of other promising molecular targeted therapy and immunotherapy will move the therapeutic modality from the all-fits-one approach for a more personalized therapeutic algorithm in the near future.

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None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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