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Histology-Driven Chemotherapy in Soft Tissue Sarcomas

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Opinion statement

Doxorubicin and ifosfamide are the two chemotherapy drugs that have consistently demonstrated activity in "soft tissue sarcoma" (STS). However, STS is not a homogeneous entity but an umbrella term for a diverse group of more than 40 differing subtypes; each with distinct underlying biology, natural history and response to treatments. The accuracy of the histological and in some cases molecular diagnosis is therefore critical to the optimal treatment of these patients. Leiomyosarcomas have been shown to have limited responsiveness to ifosfamide, but both the combination of gemcitabine and docetaxel, and single agent trabectedin have shown considerable activity in this tumour group. Differences in responses to chemotherapy are seen for leiomyosarcomas of different anatomical sites with uterine leiomyosarcoma demonstrating considerable chemo-responsiveness, whereas vascular leiomyosarcomas appearing far less sensitivity. There is considerable variation in the sensitivity of the three main subtypes of liposarcomas, with well-differentiated liposarcomas showing generalised chemo-resistance through to the impressive responses seen anthracyclines and to trabectedin with the myxoid subtype. Angiosarcomas have demonstrated considerable sensitivity to paclitaxel, a drug that has little activity outside of vascular sarcomas, and liposomal doxorubicin appears to have a particular indication in this subtype. Synovial sarcomas appear to have significant sensitivity to ifosfamide, even on re-challenge. On the other hand, there are subtypes that are chemo-resistant, including gastrointestinal stromal tumour, alveolar soft part sarcoma and clear cell sarcoma, and chemotherapy plays no role in their management. Whilst it is obvious that there is a need to find new agents to treat these tumours, there is an imperative to make sure that the studies that evaluate their "efficacy" are designed to determine the efficacy within differing histiotypes through stratification by histological subtype, or enrichment strategies to ensure that "activity" is not diluted by unresponsive or even chemo-resistant tumour types.

Introduction

Soft tissue sarcomas have, until recently, been managed to a great extent as a homogeneous tumour type, with chemotherapy comprising essentially doxorubicin and ifosfamide as either sequential single agents

or as a combination. This has been despite the increasing understanding that not only do these many histological subtypes have differing histology, they have differing natural histories and underlying biology. There has also been some evidence among the many studies of chemotherapy agents in soft tissue sarcomas in general that these entities respond differently to chemotherapy and that there is no place for a "one treatment fits all" strategy. Chemotherapy regimens including combination gemcitabine and docetaxel, weekly paclitaxel, trabectedin and liposomal doxorubicin are now part of the arsenal available for those subgroups where activity has been demonstrated. This review aims to discuss briefly some of the important histological subtypes and the evidence for the use of various chemotherapy options.

Leiomyosarcomas

Leiomyosarcomas represent one of the most common subtypes of soft tissue sarcomas and can arise anywhere in the body. Leiomyosarcoma probably represents a spectrum of diseases with significant differences in behaviour and chemo-sensitivity seen. Uterine leiomyosarcomas are very responsive to many chemotherapy agents in contrast to vascular leiomyosarcomas and non-gastrointestinal stromal tumours (GIST) visceral leiomyosarcomas, with extremity leiomyosarcomas demonstrating moderate chemo-sensitivity. The standard first-line therapy for leiomyosarcomas has traditionally been doxorubicin. Recent developments including the combination of gemcitabine and docetaxel as well as trabectedin have broadened the choice of drugs available in this group of patients.

Anthracyclines

Doxorubicin has been the standard chemotherapy for soft tissue sarcomas since the mid 1970s, either as single agent or combined with ifosfamide. Response rates for first line doxorubicin reported are 16–27% [1], although response rates as low as 10% have been reported [2]. There have been many studies comparing single agent doxorubicin with a variety of combination therapies, but it is still controversial whether the improved response rates seen, in particular with the combination of doxorubicin with ifosfamide, translate into improved survival. The European Organization for Research and Treatment of Cancer, Soft Tissue and Bone Sarcoma Group (EORTC STBSG) have recently completed recruitment to a large randomised study comparing doxorubicin with or without ifosfamide and the results of this should answer this question.

Whilst doxorubicin has clearly been shown to demonstrate efficacy in soft tissue sarcomas, it is clear that there are cohorts of patients more or less likely to benefit. Many studies evaluating anthracyclines in the first line setting have been performed by the EORTC STBSG. A review of the approximately 2,200 patients enrolled into these studies evaluated the prognostic variables [3]. Predictors of survival included young age, good PS, no liver metastases, and low grade, and for response young age, absence of liver metastases, high grade and liposarcomas. Although not statistically significant leiomyosarcomas appeared to have poorer response rates to anthracyclines compared to other histological subtypes. These studies were performed prior to the recognition that most gastrointestinal leiomyosarcomas were in fact gastrointestinal stromal tumours which are intrinsically chemo-resistant.

Ifosfamide

Ifosfamide has been found to have essentially equivalent response rates in the first line to doxorubicin, with response rates in the range of 20–25% for soft tissue sarcomas in general [4]. It is less convenient to the patient as it generally requires hospitalisation and so is usually given as second line therapy or in combination with doxorubicin in the first-line setting.

Sleijfer et al. [5••] undertook a retrospective review of the EORTC STBSG database to determine prognostic and predictive variables for ifosfamide in soft tissue sarcoma. There were more than 1,300 patients treated in first-line studies with ifosfamide or ifosfamide-containing regimens. Patients who had received single-agent doxorubicin were used as the comparator for predictive value analysis. The median progression-free survival was 19 weeks. Leiomyosarcoma conferred a poorer outcome in terms of risk of death in the univariate but not multivariate analyses compared with other histologies In the predictive factor analysis patients with leiomyosarcomas treated with ifosfamide had poorer overall survival compared to those treated with doxorubicin ($p=0.0247$) and a non-significant trend was seen towards a poorer response rate.

Gemcitabine and Docetaxel

Single-agent gemcitabine has shown limited activity in soft tissue sarcomas in general, although responses were seen in patients with leiomyosarcoma [6, 7]. Patel et al. [8] reported an 18% ($n=7$) response rate in a study of 31 soft tissue sarcomas, with four of the 10 of the leiomyosarcomas responding. Most of these studies utilised a 30-min infusion, but there is good pharmacological data to suggest that a more prolonged fixed-rate dose would be more active. Gemcitabine is converted to the active metabolite, gemcitabine triphosphate, in the cell. This conversion is a saturable process and at shorter infusion rates, not all of the pro-drug is converted to active drug. Several studies have shown that prolonging the infusion allows accumulation of the active drug with saturation occurring at a gemcitabine plasma concentration of 20 μmol/L [8, 9]. This concentration is achieved with a fixed-dose rate of 10 mg/m^2/min. One small study utilising this regimen demonstrated some activity in leiomyosarcomas with three responses seen in patients with leiomyosarcoma [10].

Docetaxel has limited to no activity in soft tissue sarcomas [11], with the possible exception of angiosarcomas (see below); however, when combined with gemcitabine, considerable activity is seen as discussed below.

Hensley et al. [12••] reported on a small phase II study of gemcitabine given as a 90-min infusion on days 1 and 8 and docetaxel on day 8 (with G-CSF support) in 34 patients with leiomyosarcoma. Patients who had received prior pelvic radiotherapy had dose reduced regimens due to the profound bone marrow suppression of the regimen. The majority of patients (85%) had a uterine leiomyosarcoma, and just under half had received prior chemotherapy. The overall response rate was 58% and no difference seen in those who had received prior chemotherapy. The 6 month progression free rate was 47%, and median overall survival is 17.9 months. All of the

responses occurred in patients with uterine leiomyosarcoma. Sarcoma Alliance for Research through Collaboration performed a randomised phase II second line study in 122 patients with soft tissue sarcoma comparing fixed-rate dosed gemcitabine alone or with docetaxel [13•]. The primary endpoint was tumour response (partial response and complete response and stable disease lasting at least 24 weeks) and was 32% for the combination and 27% for gemcitabine alone. The partial response rate for the combination was only 16% for the combination but superior to gemcitabine (8%). Within the leiomyosarcoma group, only one of nine who received gemcitabine had a partial response compared with five of 29 in the combined arm. Both median progression free and overall survivals were significantly greater for the combined arm for the group as a whole.

Uterine leiomyosarcomas would appear to be exceptionally sensitive to the combination of gemcitabine and docetaxel [12••]. The Gynecology Oncology Group has performed a series of non-randomised studies evaluating the first-line, second-line and adjuvant activity of this combination in uterine leiomyosarcomas [14–16]. The first-line study demonstrated an objective response rate of 35.8% and stable disease in 26.2% in 42 women with advanced or metastatic uterine leiomyosarcomas [14]. The 3- and 6-month progression-free rates were 59.5% and 40.5%, which correlate highly with the criteria for determination of activity of drugs in soft tissue sarcomas as proposed by the EORTC STBSG [17••]. The median overall survival was 16.1+months. The second-line study found the objective response rate to be 27%, with 6.3% of patients achieving a complete response [15]. In addition, half of the patients achieved stable disease for a clinical benefit rate of 77%. The overall median progression-free survival was 6.7+months and for those who responded it was 9+months and median overall survival was 14.7 months. The 3- and 6-month progression-free rates were 73% and 52%, again consistent with considerable activity in the second-line setting [17••].

Trabectedin

Trabectedin is a unique anticancer drug, acting through covalent binding to the minor groove of DNA inhibiting transcriptional activity. It has demonstrated activity in soft tissue sarcomas and has recently been licenced in Europe for patients with anthracycline-resistant soft tissue sarcomas. A first-line study of trabectedin given as a 24-h infusion demonstrated an objective response rate of 17.1%, with a median duration of response of 16.5 months [18]. The EORTC STBSG performed a non-randomised study in pre-treated patients, with at least a quarter of the patients having received two or more previous lines [19]. Ninety-nine patients were treated with an objective response rate of 8%. However, 48% of patients had stabilisation of disease as best response and in 26% this lasted more than 6 months. The 3- and 6-month progression-free survival rates were 52% and 29%, respectively. Whilst the radiological response rates appear to be disappointing, the progression-free rates were very much consistent with EORTC criteria for activity in soft tissue sarcomas [17••]. Particular histological subtypes, liposarcomas, leiomyosarcomas, and synovial sarcomas appear to be more sensitive to trabectedin. The progression arrest (partial response and stable

disease) rate within the leiomyosarcoma cohort was 56%. The Trabectedin Global Sarcoma Study Group performed a randomised study comparing 3 versus 24-h infusion in pre-treated patients with leiomyosarcomas or liposarcomas [20•]. The 24-h infusion was significantly superior to the 3-h infusion for time to progression (3.7 vs. 2.3 months) and objective response rate (5.6% vs. 1.6%). This study confirmed the activity of trabectedin, especially as a 24-h infusion, in both leiomyosarcomas and liposarcomas with the 3-month progression-free survival rate in this pre-treated cohort being 51.5%, and the 6-month progression-free survival rate was 35.5%.

Liposarcomas

Liposarcomas are a common subgroup of soft tissue sarcomas comprising at least three very distinct subtypes. Well-differentiated and poorly-differentiated liposarcomas are the most common subgroup of liposarcoma and are characterised by a 12q14-15 amplification involving the MDM2 gene [21]. Myxoid liposarcomas represents approximately one third of all liposarcomas and 10% of all soft tissue sarcomas [22]. They are characterised by FUS-CHOP translocation. Myxoid liposarcomas will often have varying degrees of round cell component, which carries the same translocation as myxoid liposarcoma and is now considered to be the high-grade component of myxoid liposarcoma. The third variant is pleomorphic liposarcomas, which represents only 5% of this group of tumours.

Doxorubicin

There is little doubt that well-differentiated liposarcoma has little to no chemo-sensitivity, whereas the other subtypes, myxoid liposarcoma in particular, have demonstrated chemo-sensitivity [23•, 24]. Jones et al. [23•] reported the outcomes for 88 patients with liposarcoma treated with chemotherapy at the Royal Marsden Hospital. Sixty-four percent of the patients received doxorubicin in the first line, either as single agent or in combination with ifosfamide. The response rate for those patients with myxoid liposarcoma was 48% compared with 18% for the others ($p=0.012$), demonstrating considerable anthracycline sensitivity for this subtype. Pleomorphic liposarcomas were also shown to have significant chemo-sensitivity with a response are of 33%, and de-differentiated liposarcomas had a 25% response rate. No responses were seen in the well-differentiated cohort. Patel et al. [24] analysed those patients with myxoid liposarcomas that had received chemotherapy at the MD Anderson Cancer Centre from1986 to 1992. Eighteen of the 20 patients evaluable for response received doxorubicin and dacarbazine, with a response rate of 44%, including one complete response. Whilst retrospective, these data strongly suggest that doxorubicin has considerable activity in myxoid liposarcomas and probably pleomorphic liposarcomas.

Ifosfamide

Ifosfamide is an active agent in liposarcomas. The analysis of the EORTC STBSG database of prognostic factors predictive of outcome to first line ifosfamide showed that liposarcomas are sensitive to ifosfamide [5••]. Patients

with liposarcoma had improved survival compared with leiomyosarcoma, both in terms of risk of death, and progression-free survival. However, compared to those treated first line with doxorubicin, those receiving ifosfamide were less likely to respond.

Trabectedin

As discussed above, trabectedin has demonstrable and durable activity in soft tissue sarcomas, and leiomyosarcomas and liposarcomas in particular. In the first-line study, nine patients had liposarcomas, and of these three responded (all myxoid) [18]. These responses made up half of all of the responses seen. The EORTC study in pre-treated patients showed activity in liposarcomas with a progression arrest rate of 40% [19]. What has now become obvious is that myxoid liposarcomas are exquisitely sensitive to trabectedin. A review of 51 patients with myxoid liposarcomas treated with trabectedin in an international compassionate usage programme reported a remarkable objective response of 51% [25••]. The 3- and 6-month progression-free rates were 92% and 88%, respectively, with a median progression-free survival of 14 months. A longer-term follow-up from a single institution confirmed these results, and that with a median follow-up of 24 months the median overall survival had not been reached [26]. The biological reason for the particular sensitivity of this subtype is not understood, but may relate to inhibition of transcription of the FUS-CHOP oncogene.

Angiosarcoma

Angiosarcomas are a very rare (<2%) subgroup of soft tissue sarcomas [27]. Even within this entity, there appears to be distinct subtypes, with differing presentations, outcomes and chemosensitivity. These are angiosarcoma of scalp, primary breast angiosarcoma, cutaneous angiosarcoma, radiation induced angiosarcoma, angiosarcoma arising in places of chronic lymphoedema and vinyl chloride induced angiosarcoma of the liver [28]. There is evidence to suggest that those patients with scalp angiosarcoma have a better outcome for both response to chemotherapy and survival compared with those with disease originating below the clavicle [29, 30].

Doxorubicin and Ifosfamide

Whilst there is little published prospective data about specific response to doxorubicin or ifosfamide, there is little doubt that angiosarcomas are sensitive, in particular to doxorubicin. There are some retrospective data supportive of sensitivity to doxorubicin and possibly ifosfamide. Fayette et al. [28] reported on 61 angiosarcoma patients who received chemotherapy, with the majority receiving either doxorubicin or ifosfamide, or both. Of the 17 patients with response data the overall response rate was 59%. Fury et al. [29] reported on the MKSCC experience of 52 patients treated with at least one line of a variety of chemotherapy regimens. The activity of the chemotherapy regimen was assessed by progression-free survival (PFS), and the combination of doxorubicin with ifosfamide was the found to be the most efficacious (5.4±0.0 months) and useful activity was also seen for single-

agent doxorubicin (PFS 3.7±1.3 months). However ifosfamide was essentially inactive (PFS of 1.6±0.2 months).

Liposomal Doxorubicin

Liposomal doxorubicin has a significantly different pharmacokinetic profile, with prolonged half-life compared with standard formulation doxorubicin. In soft tissue sarcomas in general, it has been found to have equivalent efficacy to doxorubicin with a tolerable toxicity profile including no cardiotoxicity [2, 31]. Although there have been no prospective studies of liposomal doxorubicin in angiosarcoma there are pharmacokinetic and clinical data that supports its use in this tumour type.

In vivo studies in mice have shown accumulation of liposomal doxorubicin in the skin which may be the reason for the significant skin toxicity seen with this drug [32]. This cutaneous accumulation potentially provides an advantage in the treatment of angiosarcomas, as they frequently arise in the skin. Liposomal doxorubicin has also demonstrated considerable activity in Kaposi's sarcoma, another subtype of haemangiosarcoma [33].

There has been several case reports suggesting that liposomal doxorubicin is an active agent in angiosarcoma [34, 35]. Skubitz et al. [36] published a single institute's experience of liposomal doxorubicin and paclitaxel. Three of six patients treated with liposomal doxorubicin attained a partial response and a further two had a durable stabilisation of disease. The data from MKSCC also demonstrated significant activity for liposomal doxorubicin with a PFS of 4.2±0.8 months in its cohort of patients [29].

One other potential advantage of liposomal doxorubicin is the lack of cardiotoxicity [31]. This is particularly relevant in considering palliative treatment options in a group of patients who are elderly as is often the case, especially in those with scalp and neck angiosarcoma.

Taxanes

The initial phase II studies evaluating paclitaxel in advanced soft tissue sarcomas demonstrated disappointing activity in this group as a whole [37, 38]. SWOG reported an overall response rate of only 12.5% [37]. Casper et al. [38] reported the results of a single centre study of 28 patients, with only two responses seen. In both of the studies, a response was seen in a patient with angiosarcoma.

The hint of activity in angiosarcomas seen in these studies led to increased use of paclitaxel, either as a three-weekly infusion or as a weekly regimen, as demonstrated by several retrospective reviews of activity. Fata et al. [27] reported on nine patients with scalp angiosarcoma treated with either weekly or three-weekly regimens with all but one patient responding (four complete responses and four partial responses) or a median duration of response of 5 months. Skubitz [36] reported on eight patients of whom five had a major response. Fury et al. [29], in the review of the 125 patients treated at the MSKCC found that the median PFS when treated with paclitaxel was 4.0±0.7 months. Outcome was the same for paclitaxel regardless of whether given as first line or subsequent therapies. This study found that for those patients with scalp angiosarcoma weekly paclitaxel was more effective than three-weekly paclitaxel, but not for those patients with disease below the clavicle.

A retrospective analysis of patients with angiosarcoma treated with paclitaxel at 10 centres of the EORTC STBSG group between 1996 and 2005 demonstrated an impressive overall response rate of 62%, with a clinical benefit of 78% in the 32 patients identified [30]. In this study as well, disease below the clavicle was associated with poorer outcome. This study also showed improved outcome with paclitaxel for those with disease above the clavicle with a response rate of 75% compared with disease below the clavicle where the response rate was 58%. The median time to progression for whole cohort was 7.6 months. Once again, the median time to progression was better for those patients with primary head and neck angiosarcoma, 9.5 versus 7 months.

There is now prospective data from the phase II ANGIOTAX study by the French Sarcoma Group evaluating weekly paclitaxel in 27 patients [39••]. The primary endpoint of the study was the non-progression rate at 8 weeks, which was determined to be 74%. The progression-free survival at 4 months was 45%, with a median overall survival of 8 months. The objective response rate was 18.5%, which is significantly more modest than that seen in the above retrospective studies. One third of the patients had received prior anthracycline treatment, and although the numbers of patients are small, the data suggests that prior treatment does not impact on outcome.

The EORTC performed a small multicentre phase II study of docetaxel in heavily pre-treated patients and there was preliminary evidence of activity with a partial response rate of 17% and clinical benefit rate (PR and SD) of 48% [40]. Subsequently the EORTC then performed a randomised phase II study comparing docetaxel versus doxorubicin in the first- and second-line setting, and the study closed early as no responses were seen within the docetaxel arm [11]. There are many case reports and small case series of docetaxel either three-weekly or weekly regimens demonstrating activity in the literature, although what advantage it offers over paclitaxel is uncertain.

Synovial Sarcomas

Synovial sarcomas are an uncommon subtype of soft tissue sarcoma accounting for only 5–10% of the total. This entity is characterised by specific translocations SYT-SSX1 or SYT-SSX2 oncogenes. The median age of patients is approximately 33 years of age, considerably younger than for soft tissue sarcomas in general and is the most common non-rhabdomyosarcoma soft tissue sarcoma in the paediatric population. The most common site of metastatic spread is lung with liver being an unusual site [41].

Doxorubicin and Ifosfamide

Synovial sarcomas are recognised to be a chemo-sensitive subtype of soft tissue sarcomas with significant responses seen for anthracyclines, ifosfamide and trabectedin.

Synovial sarcomas are regarded as particularly sensitive to ifosfamide. This supposition is based on small studies in soft tissue sarcomas, none of which were designed to determine responsiveness according to histological subtype, either through stratification or patient cohort enrichment [42, 43].

A small series of 13 patients with metastatic synovial sarcoma treated with high dose ifosfamide demonstrated objective radiological responses in all patients, including four complete responses [44]. There is some evidence that even in those patients who have progressed previously on standard dose ifosfamide that sensitivity can be regained with re-challenge using higher doses of ifosfamide [43, 44].

The data from the retrospective review of 1,331 patients who were treated in EORTC first line trials of ifosfamide regimens confirms the significant activity of ifosfamide in synovial sarcomas [5••]. Synovial sarcomas conferred a significantly better progression-free survival outcome than leiomyosarcoma, and had a statistically higher response rate (OR 3.116; 99% CI, 1.435–6.765) to ifosfamide than leiomyosarcoma. Predictive variables showed a non-significant trend toward improved response rates compared with first line doxorubicin but no survival advantage.

A single-centre review of outcomes in approximately 100 patients with advanced synovial sarcoma found a median overall survival of 22 months, significantly higher than the median of approximately 1 year for soft tissue sarcomas in general [41]. Patients were treated with a variety of drugs in the first line but the majority received doxorubicin and/or ifosfamide. Approximately one third received the combination of doxorubicin and ifosfamide. The response rates for single-agent doxorubicin and ifosfamide were both 25%, but when combined the response rate was higher at 58%. Studies comparing single-agent doxorubicin with the combination of ifosfamide and doxorubicin have confirmed the exquisite sensitivity of synovial sarcomas to the combination [42]. Given the fact that many of the patients with synovial sarcoma are young they are more likely to tolerate and benefit from the combination.

Trabectedin

The first-line study of trabectedin in soft tissue sarcoma [18] recruited only one patient with synovial sarcoma and this patient achieved a durable partial response lasting more than a year. In the phase II study performed by the EORTC in pretreated patients, 17% of the patients had synovial sarcomas [19]. Radiological response was seen in one patient with synovial sarcoma; however, the progression arrest rate was significant at 61% consistent with clinically useful activity.

Chemo-resistant Subtypes

There are several subtypes of soft tissue sarcoma that are intrinsically chemoresistant. Examples include GIST, alveolar soft part sarcomas, clear cell sarcomas, well-differentiated liposarcomas, malignant solitary fibrous tumours and low-grade endometrial stromal sarcomas and chordomas. There are established treatments available for GIST with the impressive and durable responses seen with imatinib, sunitinib and other tyrosine kinase inhibitors.

Novel Agents in Soft Tissue Sarcomas

This is an area of considerable interest as the limitations of chemotherapy in soft tissue sarcomas have become increasingly recognised over the last de-

cade. Clearly, a full discussion of this area is beyond the remit of this review; however one agent, pazopanib warrants a brief discussion as it has demonstrated significant activity in particular histological subtypes of soft tissue sarcoma.

Pazopanib is an oral tyrosine kinase inhibitor with potent inhibition of VEGFR, as well as PDGFR and KIT. The EORTC STBSG performed a phase II study of pazopanib 800 mg daily in soft tissue sarcomas with 12-week progression-free rate as the primary endpoint [45••]. Patients were recruited into four separate histological cohorts (leiomyosarcomas, synovial sarcomas, liposarcomas, other soft tissue sarcomas). Utilising a Simon two-step testing procedure within each cohort activity for individual subgroups was determined. Recruitment was stopped at the first step analysis for the liposarcoma cohort as the definition for activity to allow completed recruitment was not met but the other three cohorts did met the definition and went on to complete recruitment. Significant and clinically relevant progression-free rates at 12 weeks were achieved for leiomyosarcomas (44%), synovial sarcomas (49%) and for the "others" cohorts (39%), with hints of improved overall survival and progression free survival compared with historical controls. The EORTC STBSG subsequently went on to perform a randomised placebo controlled study in these sensitive subtypes and with recruitment now completed, the final results are eagerly awaited.

Summary

The axiom that the standard for first line treatment is single agent doxorubicin still holds true in 2011; with the possible exception of angiosarcomas where paclitaxel is increasingly being used in the first line. The question of the role of the combination of doxorubicin and ifosfamide remains contentious, with the outstanding question of response versus survival outcomes awaiting maturity of the data from the EORTC STBSG randomised study comparing single-agent doxorubicin with the combination. In addition, there is some argument that with the publication of the retrospective review of the EORTC database suggesting inferiority of survival outcome for the use of ifosfamide first line in patients with leiomyosarcomas [5••], that this combination is no longer an appropriate regimen in this subtype. Again, the results of the randomised study may go some way to answering this issue as well.

This review has attempted to demonstrate that beyond doxorubicin the drugs to be used in soft tissue sarcoma depend critically on the histological subtype.

For patients with leiomyosarcomas, the combination of gemcitabine and docetaxel would be an appropriate second-line therapy if the patient had a good performance status [12••–15]. However, there are instances where one would consider using it as first line therapy [12••, 14]. An example would be a young patient with progressive uterine leiomyosarcoma where previously the consideration would have been for the use of the combination of doxorubicin and ifosfamide. In those patients who maintain reasonable performance status, trabectedin should be considered as third line therapy after failure with gemcitabine and docetaxel, or as a second line in those

patients who may not be medically well enough to tolerate this combination [18–20•]. As discussed above, the role of single-agent ifosfamide is uncertain, but certainly there is no evidence that ifosfamide is inactive in leiomyosarcomas, rather that it is inferior in the first-line setting compared with anthracyclines in this histological subtype.

For liposarcomas, the subtype is vital to determining therapeutic strategy. While there is no role for chemotherapy for well-differentiated liposarcomas, the chemo-sensitivity seen with myxoid liposarcomas provides opportunities for different chemotherapy regimens. Doxorubicin would remain standard first-line therapy in this group, and impressive durable responses seen with trabectedin provide an excellent second line therapy for this group of patients [25••, 26]. Single-agent ifosfamide is an active agent and so should also be considered as an appropriate second or subsequent line therapy.

Synovial sarcomas are regarded as one of the more chemo-sensitive subtypes, with some evidence for particular sensitivity to ifosfamide [5, 42, 43]. Whilst single-agent doxorubicin remains standard first line therapy, there would be an argument for combining it with ifosfamide particularly in the young patient with advanced or progressing disease [42]. Again, trabectedin [19] would represent the appropriate second line if combination therapy had been used as first line, or third line after sequential single-agent doxorubicin followed by ifosfamide.

Whilst there has been no randomised study of doxorubicin versus paclitaxel in angiosarcomas, the toxicity profile and high and durable response rates reported in the literature makes weekly paclitaxel a commonly used first-line therapy particularly in the older patient with cutaneous disease. Doxorubicin is very active in this disease [28, 29], and there is a pharmacokinetic argument [32] as well as toxicity argument for the use of liposomal doxorubicin in this subtype [29, 34–36].

Why is it that many agents that initially were not regarded as active are now utilised very efficaciously in specific histological subtypes? There are two potential reasons. The first is that response rate, whether WHO or RECIST, was utilised as the primary endpoint indicative of activity, whereas it is now recognised that there are other potentially more clinically useful endpoints such as the progression-free rate criteria of the EORTC STBSG [17••]. A recent retrospective review of potentially new agents evaluated over the last decade, utilising progression-free rates as the endpoint has really confirmed activity of agents in particular subtypes and that activity based on progression free rates is more clinically relevant [46]. As is really patently clear from the above discussion, it is critical to ensure that studies are designed to allow statistically relevant analysis of the effect of histological subtype on activity of a new drug. Stratification for histological subtype, with two-step design ensuring that too many patients with resistant subtypes are exposed to ineffective treatment is increasingly being used to evaluate new agents, such as pazopanib [45••], and this design should be incorporated into future phase II studies. Where there is clearly activity seen for a subtype, it is vital that randomised studies evaluating the true role of these agents should be attempted. What this needs is multicentre and multinational studies, and more importantly is that all eligible patients are offered entry into studies in order to answer these questions. It is only through clinical trials that new agents are licenced, and the appropriate role of these and more

established agents can be determined and it is behoven on all sarcoma oncologists to ensure that these studies do recruit.

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