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Recent Developments in Salvage Chemotherapy for Patients with Metastatic Soft Tissue Sarcoma

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Abstract

The number of effective cytotoxic agents for the treatment of patients with metastatic adult soft tissue sarcoma is limited, especially when patients have failed anthracycline- and ifosfamide-based chemotherapy. For the subgroup of patients with inoperable gastrointestinal stromal tumour (GIST), progress has been made via the rapid development and approval of the targeted therapy imatinib. Small round cell tumours (SRCTs), such as Ewing's sarcoma/primitive neuroectodermal tumour, desmoplastic SRCT and rhabdomyosarcoma, are chemotherapy-sensitive and potentially curable malignancies, which are treated with multimodality, dose-intensive, neoadjuvant protocols regardless of size or overt metastatic disease. Most other high-grade (grading >I), so-called 'adult type', soft tissue sarcomas such as fibrosarcoma, liposarcoma, pleomorphic and synovial sarcomas are treated with an anthracycline-based regimen with or without ifosfamide as front-line therapy. In relapsed 'adult type' soft tissue sarcomas, trofosfamide, gemcitabine and trabectedin (ecteinascidin 743) appear to be drugs associated with some activity and an acceptable toxicity profile. A high activity has been reported for the taxanes, in particular for paclitaxel, in vascular sarcomas located in the scalp or face and in Kaposi's sarcoma. It is interesting to note that the different drugs have particular effects in distinct subtypes of soft tissue sarcoma; however, it should be taken into account that the number of patients included in the phase II trials is limited. The role of the newer agents (e.g. epothilones, brostallicin) is currently undefinable. Targeted therapy inhibiting vascular endothelial growth factor receptor, epidermal growth factor receptor, RAF kinase, c-KIT or platelet-derived growth factor receptors will continue to be tested in GIST patients refractory to imatinib and in other sarcoma histologies.

Soft tissue sarcomas are malignant tumours arising from mesodermal tissues. They consist of a wide variety of histological subtypes that differ in terms of biological behaviour, prognosis and response to different treatment modalities. There are distinct biological differences among certain subtypes of soft tissue sarcomas, and these differences need to be taken into account at the time of therapeutic decision-making.[1] Leiomyosarcomas originating in the gastrointestinal tract (the majority of which are now classified as gastrointestinal stromal tumours [GISTs]) are refractory to standard chemotherapeutic agents such as doxorubicin and ifosfamide, whereas uterine and retroperitoneal leiomyosarcomas have shown definite sensitivity to these agents.[2] For the subgroup of patients with inoperable GIST, progress has been made by the rapid development and approval of the targeted therapy imatinib (STI 571). Small round cell tumours (SRCTs), such as Ewing's sarcoma/primitive neuroectodermal tumour (PNET), desmoplastic SRCT and rhabdomyosarcoma, are chemotherapy-sensitive and potentially curable malignancies, which are treated with multimodal, dose-intensive, neoadjuvant protocols regardless of size or overt metastatic disease.[3,4] Most other high-grade (grading >I) – so-called 'adult type' – soft tissue sarcomas such as fibrosarcoma, liposarcoma, pleomorphic and synovial sarcomas are treated with a doxorubicin-based regimen with or without ifosfamide as front-line therapy. Only these drugs have shown single-agent activity producing response rates in the range of 10–30%.[5-8] An approach utilising dose intensification with the use of peripheral blood stem cell transplantation and haematopoietic growth factor support has increased response rates up to 50–60%, but no substantial impact on overall survival has been demonstrated in this heterogeneous disease to date.[9-13]

However, patients with advanced soft tissue sarcoma histology still have a very poor prognosis when progressing during or shortly after first-line chemotherapy. Established drugs for second-line chemotherapy after progression during or after doxorubicin are ifosfamide (10–14 g/m^2 per cycle) and dacarbazine.[14,15] Therefore, salvage therapy options after failure of front-line therapy are limited to patients with good performance status, younger age, and normal renal and hepatic function. Potential active drugs with different mechanisms of action have been investigated, such as taxanes, antimetabolites, alkylating agents, new marine compounds, DNA topoisomerase I inhibitors and minor groove binders. In this review we summarise the drug development in this setting over the last 5 years, including the published literature (from PubMed – National Library of Medicine) as well as recent meeting data (Connective Tissue Oncology Society, American Society on Clinical Oncology, European Society on Medical Oncology, European Conferences on Clinical Oncology and European Organisation for Research and Treatment of Cancer [EORTC] group meeting of the Soft Tissue and Bone Sarcoma Group [STBSG]) on soft tissue sarcoma. Searches were conducted using the terms 'soft tissue sarcoma', 'chemotherapy' and 'refractory'.

1. Taxanes

The Southwest Oncology Group (SWOG) reported a trial of paclitaxel in patients with previously untreated advanced soft tissue sarcomas, revealing a response rate of 12.5%.[16] In a recently published phase II trial paclitaxel was evaluated in patients with recurrent or advanced leiomyosarcoma of the uterus. Fifty-three patients were entered and 48 patients were evaluable for toxicity and response. Fifteen patients had received prior irradiation and only 39 patients had been treated with first-line chemotherapy. A median of two (range 1–12) courses of paclitaxel were applied. Four (8.4%) patients had a complete or partial response and 22.9% patients had a stable disease demonstrating that single-agent paclitaxel has modest activity in previously treated uterine leiomyosarcoma.[17] Furthermore, on the basis of phase II trial results, paclitaxel is highly effective in

AIDS-related Kaposi's sarcoma as well as in angiosarcoma of the scalp or face. Fata et al.[18] reported eight of nine patients responding to paclitaxel (four partial responses and four clinical complete responses).

Reports from an EORTC phase II study and from an Austrian group have described five and four partial responses of 29 and 27 evaluable patients, respectively, receiving docetaxel, previously treated with chemotherapy, with response rates of 17% and 15%, respectively.[19,20] Another trial investigating docetaxel in previously untreated patients with soft tissue sarcomas reported a low response rate of 5.9% (95% CI 0.1, 29).[21] A planned randomised, phase II trial of the EORTC was prematurely closed because no response was observed among the first 25 assessable patients in the docetaxel treatment arm.[22] Results of these trials are summarised in table I.

2. Patupilone (Epothilone B) Derivatives

Ixabepilone (epothilone B analogue, BMS 247550), a semisynthetic analogue of the natural product patupilone, functions as a mitosis inhibitor analogous to that of paclitaxel (i.e. microtubule stabilisation). In a phase II study, a total of 31 patients were treated at a dose of 50 mg/m^2 given as a 1-hour infusion every 3 weeks. A low response rate of 6% was noted as well as a considerable toxicity profile (3% death rate due to sepsis, 41% grade II/IV neutropenia, 46% grade III/IV non-haematological toxicities).[23]

3. Vinca Alkaloids

Vinca alkaloids are part of studied combination regimens in childhood sarcoma. Single-agent activity was demonstrated in rhabdomyosarcoma.[48] Vinorelbine has been tested in adult type sarcoma in a single trial showing one complete and three mixed responses in 36 evaluable patients.[44]

4. Antimetabolites

While three trials found no substantial activity of gemcitabine in advanced soft tissue sarcomas,[24-26] an MD Anderson Cancer Center (Houston, TX, USA) trial demonstrated a remission rate of 18% with a median duration of 3.5 months in patients with soft tissue sarcomas other than GIST.[49] However, no objective responses were seen in 17 patients with GIST. A recently published trial of the ECOG (E1797) achieved a 4% rate of remissions in previously untreated patients (90% CI 0, 18); however, a partial response in a patient lasted for 8 months.[27] By reviewing all trials, activity was particularly observed in patients with angiosarcomas, non-gastrointestinal leiomyosarcoma or unclassified sarcomas.[24-29,49,50]

During a phase II trial at the sarcoma centre in Tuebingen, Germany, 19 patients were included to receive gemcitabine 1.0 g/m^2 as a 30-minute infusion on days 1, 8 and 15 every 4 weeks.[28] All patients had progressive disease during or shortly after an anthracycline/ifosfamide-based regimen. Four of these 19 patients did not start study treatment because of fulminant tumour progression. In the 15 patients who are assessable, a total of 62+ cycles have been applied to date (median 3, range 1–18+). The remission rate was 6% and 47% of patients achieved disease stabilisation. The median progression-free survival rate (PFR) was 3 months (range 1–18+). Eighty-seven percent of the cycles have been applied without any dose modification or delay. This series confirmed the earlier observation of a considerable number of disease stabilisations in pretreated adult soft tissue sarcoma patients with gemcitabine. The calculated PFRs at 3 and 6 months were 46.7% (95% CI 21.4, 71.9) and 13.3% (95% CI 0, 30.5).[28] Considering this criteria as the primary endpoint for phase II trials in soft tissue sarcomas,[50] gemcitabine appears to have an efficacy comparable with dacarbazine.[28]

Table I. Salvage chemotherapy in patients with soft tissue sarcoma refractory to anthracyclines

	No. of evaluable patients	CR/PR (%)	NC (%)	Comments	Reference
Taxanes					
Paclitaxel	48	12.5	NG		16
Paclitaxel	53	8.4	22.9	Uterine LMS	17
Paclitaxel	9	89		Angiosarcoma	18
Docetaxel	29	17	NG		19
Docetaxel	27	15	15		20
Patupilone (epothilone B) derivatives					
Ixabepilone (BMS 247550)	31	6			23
Antimetabolites					
Gemcitabine	18	11	33		24
Gemcitabine	32	3	NG		25
Gemcitabine	29	3	NG		26
Gemcitabine	21	4	32		27
Gemcitabine	15	6	47	6mo PFR: 13.3%	28
Gemcitabine	18	6	39		29
Minor groove binders					
Trabectdein (ET 743)		4	22.4	6mo PFR: 24%	30
Trabectdein		8	NG	12mo PFR: 9%	31
Alkylating agents					
Trofosfamide	18	0	50		32
Trofosfamide	18	18	50		33
Trofosfamide	11	0	NG		34
Temozolomide	31	3	NG		35
Temozolomide	41	5	33	Adult sarcoma	36
Temozolomide	19	0	22	GIST	36
DNA topoisomerase I inhibitors					
Topotecan	21	0	28		37
Topotecan	16	0	38		38
Topotecan	15	67	33	Combined with CPM in RMS subtypes	39
Irinotecan	5	40	NG	SRCT	40
Irinotecan	20	45	15	SRCT	41
Irinotecan	14	0	0	GIST (n = 7)	42
Rubitecan (9 NC)	39	8	25.6	Adult sarcoma	43
Rubitecan	16	0	6	GIST	43
Vinca alkaloids					
Vinorelbine	14	0	NG		44
Thymidylate synthase inhibitor					
Raltitrexed	22	0	23		45
Combination regimens					
Gemcitabine + docetaxel	34	53	20.5	Uterine LMS/LMS	46
Paclitaxel + epirubicin	27	7.4	22.2	Only 18 patients pretreated with chemotherapy	47

CPM = cyclophosphamide; **CR/PR** = complete/partial remission; **GIST** = gastrointestinal stromal tumour; **LMS** = leiomyosarcoma; **NC** = no change/disease stabilisation; **NG** = not given; **PFR** = progression-free rate; **RMS** = rhabdomyosarcoma; **SRCT** = small round cell tumour.

5. Minor Groove Binders

Trabectedin (ecteinascidin 743, ET 743) is a natural marine product derived from the tunicate *Ecteinascidia turbinata*. Phase II trials in Europe and the US have revealed a low objective response rate of approximately 5–10%, but a response duration of approximately 10 months.[51,52] In particular, anti-tumour activity has been seen in leiomyosarcoma and liposarcoma. The PFR at 6 months was 24%[30] and at 12 months was 9%.[31] The mechanism of action is not fully elucidated. Trabectedin binds to the N2 position of guanine in the minor groove of DNA with some degree of sequence specificity altering the transcription regulation of induced genes. Patients received trabectedin at a dose of 1500 μg/m^2 as a 24-hour continuous infusion every 3 weeks on an outpatient basis. Observed toxicity included mainly transient liver enzymes elevations and neutropenia, as well as rhabdomyolysis as a rare but potentially lethal toxicity. Trabectedin did not cause alopecia, mucositis, cardiotoxicity or neurotoxicity. All adverse effects were reversible and non-cumulative. The risk of developing severe toxicity appears to be substantially enhanced in patients with relatively moderate hepatic dysfunction without a coincident effect on body clearance. Co-treatment with dexamethasone seems to decrease the incidence of severe toxicity as well as the area under the concentration-time curve of the drug.[53] Further investigation in sarcomas focuses on combination trials, including standard cytostatics such as doxorubicin. A comparative phase III EORTC trial of trabectedin and ifosfamide has been launched in anthracycline-refractory uterine leiomyosarcoma.[54]

Preliminary data of an EORTC STBSG trial with brostallicin, another new minor groove binder, revealed two partial responses as well as 17 of the 42 included patients having disease stabilisation at the end of cycle two.[55]

6. Alkylating Agents

Trofosfamide is an alkylating agent that, like other oxazaphosphorine derivatives, has to be activated by hepatic cytochrome P450 oxidases. Its bioavailability is nearly 100% after oral application. The main active metabolites are 4-hydroxytrofosfamide and 4-hydroxyifosfamide. In two consecutive phase II trials including a total of 36 patients, the drug was administered at a dosage of 300 mg/day for 1 week followed by 150 mg/day given continuously. All patients had received at least one anthracycline-based chemotherapeutic regimen prior to trofosfamide. Three patients responded to treatment.[32,33] A third trial included 11 pretreated and 12 chemotherapy-naive patients with metastatic sarcomas. Doses were escalated every third week until the development of grade II leukopenia. The daily dose that produced grade II leukopenia was 200–250mg in 65% of the patients. Three patients attained a partial response, all of whom had received trofosfamide as first-line treatment.[34] In all three studies the toxicity profile was found to be low.

Temozolomide is also an oral alkylating agent, but is derived from imidazotetrazine. It exhibits broad-spectrum antitumour activity against murine tumours.[56] It was developed as a potential alternative to dacarbazine.[15] Compared with dacarbazine, temozolomide was found to offer a comparable antitumour activity, good oral bioavailability and a better toxicity profile.[57] The active metabolite is the linear triazine monomethyltriazenoimidazole carboxamide (MTIC). Cytotoxicity of MTIC is believed to be because of alkylation at the O-position of guanine, with additional alkylation occurring at the N-position.[58] Whereas dacarbazine requires metabolic activation by the liver, temozolomide degrades into MTIC at physiological pH. Currently used application schedules are either 85 mg/m^2/day for 21 days or 750 mg/m^2 in divided doses over 5 days, both on a 28-day cycle. Both regimens resulted in few grade III or IV toxicities. An objective response rate of 10% was found in three studies examining temozolomide for advanced soft tissue

sarcomas. However, some further activity was noted in patients with leiomyosarcomas.[35,36,59]

7. DNA Topoisomerase I Inhibitors

As a DNA topoisomerase I inhibitor with its potential activity against tumours with slow proliferation and refractoriness to other drugs,[60] topotecan is considered to be a promising new substance to be evaluated in advanced metastatic sarcoma. The National Cancer Institute of Canada found a 10.3% remission rate (95% CI 2.2, 27.4) for topotecan in 29 untreated patients.[61] On the basis of the hypothesis that prolonged exposure to the S-phase-specific agent topotecan would be more efficacious in the treatment of soft tissue sarcomas, the SWOG performed a phase II trial of topotecan administered as a continuous infusion in adult patients with untreated advanced soft tissue sarcomas. Topotecan at a dosage of 0.5 mg/m^2/day was applied on days 1–21 of repeated 28-day cycles. No objective responses were observed (95% CI 0, 16) in 21 eligible patients.[37]

Another phase II trial of topotecan in pretreated adult patients revealed no objective remission in 16 patients.[38] Sixty-two percent of the patients had progressive disease at the first response evaluation, while only 38% of the patients achieved a disease stabilisation lasting for 6 weeks. The calculated PFRs at 3 and 6 months were 31.3% (95% CI 10.0, 52.5) and 6.3% (95% CI 0, 18.1), respectively, and the median overall survival time was 5.5 months (range 1.5–13.5 months). Conversely, topotecan was well tolerated despite severe but uncomplicated grade III/IV neutropenia in 67% of patients. Considering the PFR, topotecan appears to be rather ineffective in pretreated adult soft tissue sarcoma. Topotecan is currently being investigated as an addition to standard chemotherapy in paediatric sarcoma patients with unfavourable histology, advanced disease or in case of relapse.[38] In recurrent or refractory rhabdomyosarcoma, 10 of 15 paediatric patients attained a response to the combination of cyclophosphamide and topotecan.[39]

Irinotecan has proven activity in SRCT, which might be schedule dependent. A high inhibition of tumour growth was found when rhabdomyosarcoma xenografts were given in protracted low-dose schedules. A retrospective analysis of eight patients with relapse after previous stem cell transplantation salvage chemotherapy consisting of irinotecan 20 mg/m^2/day on days 1–5 and days 8–12, repeated twice with 3-week cycles, was associated with acceptable gastrointestinal toxicity. Among five patients with measurable diseases based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, two partial remissions (one rhabdomyosarcoma and one Ewing's sarcoma) were observed.[40] The Children's Oncology Group[41] performed a phase II window trial in paediatric patients with metastatic rhabdomyosarcoma. A partial response rate of 45% was observed after two cycles (95% CI 23, 67).[41] In 'adult type' sarcoma patients there is one report available showing no objective response in 14 patients.[42] However, one-half of the patients entered in the trial had a histology of a GIST that most likely might have affected the results of this small phase II trial.

The insoluble compound rubitecan (9-nitro-20-(S)-camptothecin, 9 NC), a derivative of the plant alkaloid camptothecin, has been shown to be an inhibitor of DNA topoisomerase I.[62] Initial molecular studies showed that it inhibits DNA synthesis and causes DNA strand breaks. Exposure of U-937 human myeloid leukaemia cells to irinotecan, rubitecan or IDEC 132 (9-aminocamptothecin) resulted in an 80- to 100-fold increase in expression of *c-jun* and *junB* messenger RNAs, followed by a characteristic degradation of cellular DNA.[63] This action could contribute to the regulation of DNA repair mechanisms and, in the event of irreparable damage, to the initiation of programmed cell death. In preclinical studies, rubitecan was found to be highly inhibitory to several human tumours in tissue culture and to xenografts in animals. In a phase I clinical trial, 29 patients with various neoplasms were treated with rubitecan at 1, 1.5 or 2 mg/m^2/day

on a 5-day treatment, 2-day rest schedule. The dose-limiting toxicity was haematological; the next most frequent and significant toxicities were gastrointestinal. In addition, chemical cystitis was observed in 23% of patients. The recommended dosage for phase II was 1.5 mg/m^2/day for patients with one pretreatment or no prior therapy.[64] Rubitecan was investigated at the MD Anderson Cancer Center during a two-arm phase II trial.[43] Patients with leiomyosarcomas of the gastrointestinal tract (GIST) comprised one arm, and patients with other soft tissue sarcoma histologies were enrolled on the other arm. Fatigue was the most common toxicity, affecting 75% of all patients (20% of all patients had fatigue as grade III toxicity), followed by nausea (66%; 4% of all patients had nausea as grade III toxicity) and diarrhoea (64%; 9% of all patients had diarrhoea as grade III toxicity). Seven percent of patients required hospitalisation for nausea, vomiting and dehydration. Three partial responses were noted among the 39 patients with different soft tissue sarcoma histologies (response rate 8% [95% CI 0, 16]). No objective responses were seen among the 16 evaluable GIST patients. One patient with liver metastases achieved a minor response that lasted <8 weeks. Of the 56 patients enrolled on the study, 14 had stable disease (median duration 4 months; range 2–8 months). Of the eight other patients with chordoma three achieved stable disease for a median of 174 days.[43] On the basis of these and other available data, a formal phase II study of rubitecan in patients with chordomas has been launched by the University of Michigan (Ann Arbor, MI, USA).

8. Inhibitor of Thymidylate Synthase

In a phase II study of the EORTC STBSG, raltitrexed was investigated in patients with advanced soft tissue sarcomas refractory to doxorubicin-containing regimens. Raltitrexed was given at 3 mg/m^2 as a 15-minute intravenous infusion once every 3 weeks. Among the 23 patients included, 22 patients were evaluable for response to therapy. Patients had previously received chemotherapy in metastatic phase or as adjuvant treatment or both. The best response was stable disease in five (23%) patients, while disease progression was noted in 17 patients (77%). Thus, raltitrexed as monotherapy is not an effective treatment for patients who failed conventional chemotherapy with doxorubicin and ifosfamide.[45]

9. Combination Regimens

Hensley et al.[46] reported on the combination of gemcitabine and docetaxel in uterine leiomyosarcoma and of leiomyosarcoma at other locations. A response rate of 53% and a median time to progression of 5.6 months was seen.[46] This is an interesting finding, since docetaxel has been associated with low activity when given as a single agent.

Another trial investigated the combination of paclitaxel 200 mg/m^2 and epirubicin 75 mg/m^2 administered every 3 weeks. Twenty-seven patients with recurrent soft tissue sarcoma entered, but only 18 patients had previously received chemotherapy. Two patients had a partial response (7.4%; 95% CI 2.6, 12.2). The median response duration was 4 months. Six patients had stable disease (22.2%). Grade III/IV toxicities consisted of neutropenia (70%), anaemia (3.7%), thrombocytopenia (7.4%) and febrile neutropenia (18.5%).[47] In recurrent or refractory rhabdomyosarcoma in paediatric patients, cyclophosphamide plus topotecan was shown to be an active combination.[39,65]

10. Phase I and Ongoing Phase II Trials

A rebeccamycin analogue with DNA topoisomerase inhibitory properties, becatecarin (NSC 655649), revealed activity during a phase I study in a patient with refractory soft tissue sarcoma.[66]

Biricodar (incel, VX 710) restores drug sensitivity to P-glycoprotein and multidrug resistance-associated protein-1-expressing cells. In a phase I/II study evaluating the safety, pharmacokinetics and efficacy of biricodar plus doxorubicin in patients

with anthracycline-resistant soft tissue sarcoma, 9 of 26 evaluable patients attained responses and seven patients had disease stabilisation with a median progression-free interval of 3.4 months.[67]

Bortezomib (PS 341), a proteasome inhibitor, is currently investigated in a two-arm study in adult patients with metastatic or recurrent sarcomas including Ewing's sarcoma, osteogenic sarcoma, rhabdomyosarcoma or other soft tissue sarcomas. The primary endpoint of this trial is the determination of the response rate. Secondary endpoints include analyses of 20S proteasome inhibition in patients' lymphocytes, urine vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) levels, tumour p53, MDM2, and cyclin D and E expression by immunohistochemistry. Twenty-three patients with different sarcoma histologies have been accrued so far. Toxicities observed include constipation/abdominal pain, myalgia and persistent neuropathy. Fatigue has been the most common adverse effect. Of 15 evaluable patients, best responses were progression in 11 and stable disease in four patients. No changes in VEGF and FGF urine levels have been observed. 20S proteasome inhibition was measured in a range of 60–65%.[68]

The EORTC STBSG is currently evaluating the DNA topoisomerase I inhibitor exatecan (DX 8951f) in refractory soft tissue sarcoma. Exatecan is a water-soluble camptothecin derivative with greater *in vivo* and *in vitro* activity than topotecan or irinotecan. Enrolment was completed at the end of 2003. For the subtype of synovial sarcomas expressing human epidermal growth factor receptor (EGFR)-1/EGFR-1 a phase II study with the EGFR inhibitor gefitinib (iressa, ZD 1839) has recently started to recruit patients in different European countries. The EORTC STBSG has also launched phase II trial with soblidotin (TZT 1027), a synthetic tetrapeptide derivative of dolastatin-10 with potent anti-tumour activity that acts by disrupting cellular microtubule polymerisation. Anti-tumour activity for soblidotin was observed in leiomyosarcoma and liposarcoma during earlier phase I studies.[69] Other therapeutics being developed in soft tissue sarcoma are cancer vaccine HSPPC-96, a heat shock protein vaccine, and GPX-100, a non-cardiotoxic analogue of doxorubicin. In addition, the concept of VEGF inhibition is currently investigated in untreated or previously treated patients using bevacizumab combined with doxorubicin (US phase II trial). Anti-bcl-2 antisense studies are also planned in different sarcoma subtypes, preferably chondrosarcoma with known high bcl-2 expression. In accordance with the clinical drug development in refractory GIST, several trials are planned in refractory adult type soft tissue sarcoma using different mechanisms of actions, such as protein kinase C inhibitors (midostaurin [PKC-412]), mammalian target of rapamycin serine/threonine kinase inhibitors (everolimus [RAD 001], temsirolimus [CCI 779]) and multi-tyrosine kinase inhibitors (SU 11248, BMS 354825, AMG 706 and sorafenib [BAY 439006]).

Vaccines and cellular targeting approaches, such as MAGE-12 peptide vaccine, tumour-specific peptide vaccination + IL-2 or heat shock protein peptide vaccine, are also being investigated in many centres. Intravenous injection of antineoplaston-A10 and -AS2-1, which are naturally occurring peptides and amino acid derivatives that control neoplastic growth by arresting the cell cycle in the G1 phase and by reducing mitosis, have been used in rare cases; however, efficacy is not proven. Rosiglitazone, a peroxisome proliferator-activated receptor-γ ligand is currently investigated in low-grade (G1) liposarcoma. However, dosage of the drugs is controversial.[70] The cyclin-dependent kinase inhibitor alvocidib (flavopiridol) is also part of trials in soft tissue sarcoma.[71] An overview of currently investigated experimental drugs is given in table II.

11. Experimental Approaches

In two of five human soft tissue sarcoma cell lines (HTB-82 rhabdomyosarcoma, HTB-91 fibrosarcoma, HTB-92 liposarcoma, HTB-93 synovial sarcoma and HTB-94 chondrosarcoma) tumour

Table II. Experimental drugs in refractory soft tissue sarcoma

Drug	Mechanism of drug action
Phase I	
Becatecarin (NSC 655649)	DNA topoisomerase I inhibitor
Biricodar (VX 710)	Restore sensitivity to P-glycoprotein, multi-drug resistance-1
Bortezomib (PS 341)	Proteasome inhibitor
Phase II	
Exatecan (DX 8951f)	DNA topoisomerase I inhibitor
Gefitinib	Epidermal growth factor tyrosine kinase inhibitor
Cancer vaccine HSPPC-96	Heat shock protein
GPX 100	Doxorubicin analogue
Oblimersen (G 3139)	Anti-bcl-2 antisense
Alvocidib (flavopiridol)	Cyclin-dependent kinase inhibitor
AMG 706, BMS 354825, SU 11248, sorafenib (Bay 43-9006)	Multityrosine kinase (VEGF[R], EGFR, c-KIT, PDGFR, RAF kinase) inhibitors
Soblidotin (TZT 1027)	Tubulin polymerisation inhibitor
Rosiglitazone	PPAR-γ ligand (low-grade liposarcoma)
Bevacizumab	VEGF antagonist
Midostaurin (PKC 412)	Protein kinase C inhibitor
Everolimus (RAD 001), temsirolimus (CCI 779)	Mammalian target of rapamycin inhibitors

EGFR = epidermal growth factor receptor; **PDGFR** = platelet-derived growth factor receptor; **PPAR-γ** = peroxisome proliferator-activated receptor-γ; **VEGF(R)** = vascular endothelial growth factor (receptor).

necrosis factor-related apoptosis-inducing ligand (TRAIL) induced significant apoptosis (>90% in HTB-92 and HTB-93 cells). These data suggest that TRAIL, either as a single agent or in combination with cytotoxic agents, might represent a new treatment option for advanced soft tissue sarcoma.[72]

12. Conclusion

The treatment of patients with anthracycline-refractory soft tissue sarcomas is complex. There are limited agents available and standard drugs in the second-line setting are associated with significant toxicity. SRCT (Ewing's sarcoma/PNET, desmoplastic SRCT, rhabdomyosarcoma), mainly developing in patients of younger age, are treated in specific protocols depending on the special subtype. SRCTs are chemotherapy sensitive and potentially curable malignancies regardless of size or overt metastatic disease. Treatment of relapsed patients with SRCT has yielded high rates of remissions with chemotherapy combinations, including DNA topoisomerase I inhibitors. In relapsed 'adult type' soft tissue sarcomas trofosfamide appears to be associated with some activity and a considerably low toxicity profile. On the basis of a small amount of data, the taxane paclitaxel has activity in Kaposi's sarcoma and in angiosarcoma. It produces remissions and disease stabilisations, even in patients pretreated with ifosfamide. Gemcitabine also has some activity, particularly in patients with non-gastrointestinal leiomyosarcoma, angiosarcoma and malignant fibrous histiocytoma. The data on prolonged gemcitabine infusions suggest improved activity based on prolonged intracellular gemcitabine levels. Trabectedin has been one of the most extensively tested agents, and its ability to slow growth kinetics of a tumour and stabilise it clinically is remarkable. Several phase II trials in Europe and in the US have consistently revealed a response rate of approximately 10%, and also a prolonged response duration of approximately 10 months. The role of the newer agents (e.g. epothilones, brostallicin) is currently not definable. Bevacizumab, SU 11248, midostaurin, everolimus, AMG-706, oblimersen (G 3139) and other drugs inhibiting VEGF(R), EGFR, c-KIT, RAF kinase or platelet-derived

growth factor receptors will continue to be tested in GIST patients refractory to imatinib and in other sarcoma histologies. Identifying key targets in specific soft tissue sarcomas will be helpful in the testing of newer molecularly targeted agents, such as EGFR1 inhibition in synovial sarcoma with gefitinib. Because of the paucity of effective agents, consideration of clinical trial participation for patients with relapsed or progressing disease is appropriate.

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