Systemic treatment options for patients with refractory adult-type sarcoma beyond anthracyclines

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For the subgroup of patients with inoperable gastrointestinal stromal tumors, progress has been made by the rapid development and approval of the targeted therapy imatinib mesylate. Small round cell sarcoma, such as Ewing/PNET, desmoplastic small round cell sarcoma and rhabdomyosarcoma, are chemotherapy-sensitive and potentially curable malignancies, which are treated with multimodality, dose-intensitive and neoadjuvant protocols regardless of size or overt metastatic disease. A limited number of effective agents available for the treatment of patients with metastatic adult soft-tissue sarcoma exists, which have failed anthracyline and ifosfamide-based chemotherapy. Most other high-grade (grading >I) so-called adult-type soft-tissue sarcomas such as fibro, lipo, pleomorphic and synovial sarcoma are treated with a anthracycline-based regimen with or without ifosfamide as front-line therapy. In this review, the therapeutic activities of drugs currently available as second-line treatment in patients with metastatic soft tissue sarcoma are summarized, providing an overview of contentious or emerging treatment issues. In relapsed 'adult-type' soft-tissue sarcomas trofosfamide, gemcitabine and ecteinascidin (ET-743) appear to be drugs associated with moderate activity and an acceptable toxicity profile. An interesting finding to be noted is that the different drugs have particular effects in distinct subtypes of soft-tissue sarcoma; however, it has to be taken into account that the number of patients included in those phase II trials are limited. The role of the newer agents (e.g. patupilone derivates, brostallicin) is currently not definable. The so-called selective therapy targeting vascular endothelial growth factor (receptor), epidermal growth factor receptor, c-kit, Raf kinase or platelet-derived growth factor receptor and bcl-2 antisensing, proteasome, protein kinase C/B, and mammalian target of rabamycin inhibition will continue to be tested in gastrointestinal stromal tumors patients refractory to imatinib mesylate as well as in selected sarcoma subtypes. *Anti-Cancer Drugs* 18:245–254 © 2007 Lippincott Williams & Wilkins.

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Introduction

Soft-tissue sarcomas consist of a wide variety of histological subtypes differing in terms of biological behavior, prognosis and response to different treatment modalities. They are malignant tumors arising from mesodermal tissues with distinct biologic differences among certain subtypes of soft-tissue sarcomas [1]. Gastrointestinal stromal tumors (GIST), the majority of which are formerly known as leiomyosarcomas originating in the gastrointestinal tract, are refractory to standard chemotherapeutic agents such as doxorubicin and ifosfamide, whereas uterine and retroperitoneal leiomyosarcomas have shown definite sensitivity to such 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 mesylate (STI571). Small round cell sarcoma (SRCT), such as Ewing/PNET, desmoplastic SRCT and rhabdomyosarcoma (RMS), are chemotherapy-sensitive and potentially curable malignancies, which are treated with multimodality, dose-intensitive, 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 fibro-, lipo-, pleomorphic and synovial sarcoma 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]. Approaches of dose intensification with the use of peripheral blood stem cell support and hematopoetic growth factors support has increased response rates up to 50–60%, but no substantial impact on overall survival could be demonstrated in this heterogeneous diseases so far [9–13]. The escalation of the anthracycline dosage is furthermore limited owing to nonhematological side effects.

Patients with advanced soft-tissue sarcoma histology, however, still have a dismal prognosis when progressing during or shortly after first-line chemotherapy. Established drugs for the second-line chemotherapy after progression during or after doxorubicin are ifosfamide

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(10–14 g/m^2 per cycle) and dacarbazine (DTIC) [14,15]. Salvage therapy options after failure of front-line therapy are therefore limited to patients with good performance status, younger age, and normal renal and hepatic organ function. Potential active drugs with different mechanisms of action have been investigated such as taxanes, antimetabolites, alkylating agents, new marine compounds, topoisomerase inhibitors and minor groove binders. This review summarizes the drug development in this setting over the last 5 years including the published literature (i.e. PubMed – National Library of Medicine) and recent meeting data on soft-tissue sarcoma.

Antimetabolites

Three trials found no substantial activity of gemcitabine in advanced soft-tissue sarcomas [16–18]; however, a MD Anderson [19] investigation has demonstrated a remission rate of 18% with a median duration of 3.5 months. On the other hand, no objective responses were seen in 17 patients with GIST. A recently published trial of the Eastern Cooperative Oncology Group 1797 achieved a 4% rate of remission [confidence interval (CI) 90%, 0–18%]. A partial response in a patient lasted for 8 months [20]. By reviewing all trials, activity was particularly observed in patients with angiosarcoma, non-GI leiomyosarcoma and unclassified sarcoma histologies [16–24].

During a formal phase II trial at the Sarcoma Center in Tübingen, 19 patients had been screened to receive gemcitabine, as a 30-min infusion in a dosage of 1.0 g/m^2 on days 1, 8 and 15 every 4 weeks. All patients had progressive disease during or shortly after an anthracycline/ifosfamide-based regimen. Four of 19 patients did not start study treatment because of fulminant tumor progression. In the 15 patients assessable, a total of 65 + cycles have been applied to date (median 3, 1–21 +). Remission rate was 6 and 47% of patients achieved disease stabilization. The median progression-free survival rate (PFR) was determined to be 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 stabilizations in pretreated adult soft-tissue sarcoma patients with gemcitabine. The calculated PFRs at 3 and 6 months were 46.7% (CI 95%, 21.4–71.9) and 13.3% (CI 95%, (0–30.5). Considering this criteria as the primary endpoint for phase II trials in soft tissue sarcomas [21], gemcitabine appears to have a efficacy comparable to dacarbacine [22].

Taxanes

Paclitaxel

Paclitaxel is highly effective in AIDS-related Kaposi sarcoma (KS) as well as in angiosarcoma of the scalp or face based on phase II results. Fata *et al.* [25] reported eight out of nine patients responding to paclitaxel (four partial responses and four clinical complete responses). The Southwest Oncology Group reported a trial of paclitaxel in patients with previously untreated advanced adult-type soft-tissue sarcomas, revealing a response rate of 12.5% [26]. 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 have been applied. Four (8.4%) patients had a complete or partial response and 22.9% had a stable disease demonstrating that single-agent paclitaxel has modest activity in previously treated uterine leiomyosarcoma [27].

Docetaxel

Reports from a European Organization for Research and Treatment of Cancer (EORTC) phase II study and from an Austrian group have described five and four partial responses out of 29 and 27 evaluable patients receiving docetaxel, previously treated with chemotherapy, for response rates of 17 and 15%, respectively [28,29]. Another trial investigating docetaxel in previously untreated patients with soft-tissue sarcomas resulted in a low response rate of 5.9% (CI 95%, 0.1–29%) [30]. A planned randomized 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 [31]. Results of the trials are summarized in Table 1 [16–20,22,24–29, 32–56].

Minor groove binders

Ecteinascidin-743 (ET-743, trabectedin) is a natural marine product derived from the tunicate *Ecteinascidia turbinata*. Phase II trials in Europe and in the US have revealed a low objective response rates of approximately 5–10%, but a response duration of approximately 10 months [57,58]. In particular, antitumor activity has been seen in leiomyosarcoma and liposarcoma. The PFR at 6 months was 24% [33] and at 12 months was 9% [34]. The mechanism of action is not fully elucidated. ET-743 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 ET-743 at a dose of 1500 μg/m^2 as a 24-h continuous infusion every 3 weeks on an outpatient basis. Observed toxicity included mainly transient liver elevations and neutropenia, as well as rhabdomyolysis as a rare but potentially lethal toxicity. ET-743 did not cause alopecia, mucositis, cardiotoxicity or neurotoxicity. All side effects were reversible and noncumulative. The risk of developing severe toxicity appears to be substantially

Table 1 Salvage chemotherapy in patients with soft-tissue sarcoma refractory to anthracyclines

	n evaluable patients	*n* CR/PR (%)	NC (%)	Author	Reference	Comments
Taxanes						
Paclitaxel	48	12.5	NG	Balcerzak	[26]	
Paclitaxel	53	8.4	22.9	Gallup	[27]	Uterine LMS
Paclitaxel	9	89		Fata	[25]	Angiosarcoma
Docetaxel	29	17	NG	Van Hoesel	[28]	
Docetaxel	27	15	15	Kostler	[29]	
Patupilone derivates						
Epithilone B	31	6		Okuno	[32]	
Antimetabolites						
Gemcitabine	18	11	33	Späth-Schwalbe	[16]	
Gemcitabine	32	3	NG	Svancarova	[17]	
Gemcitabine	26	3	NG	Okuno	[18]	
Gemcitabine	39	18	RD: 3.5 months	Patel	[19]	
Gemcitabine	21	4	32	Okuno	[20]	
Gemcitabine	15	6	47	Hartmann	[22]	6-month PFR: 13.3%
Gemcitabine	25	3	NG	Blumgart	[24]	
Gemcitabine	18	6	39	Amodio	[23]	
Minor groove binder						
ET-743		4	22.4	Yovine	[33]	6-month PFR: 24%
ET-743		8	NG	Garcia-Carbonero	[34]	12-month PFR: 9%
Alkylating agents						
Trofosfamide	18	0	50	Hartmann	[35]	
Trofosfamide	18	18	50	Kollmannsberger	[36]	
Trofosfamide	11	0	NG	Blomqvist	[37]	
Temozolomide	31	3	NG	Woll	[38]	
Temozolomide	41	5	33	Trent	[39]	Adult sarcoma
Temozolomide	19	0	22	Trent	[39]	GIST
Bendamustin	25	4	44	Hartmann	[40]	
Topoisomerase I inhibitors						
Topotecan	21	0	28	Budd	[41]	
Topotecan	16	0	38	Reichardt	[42]	
Topotecan	15	66	33	Saylors	[43]	Combined with cyclophosphamide in RMS subtypes
Irinotecan	5	40	NG	Hosono	[44]	'Small cell sarcomas'
Irinotecan	20	45	15	Pappo	[45]	'Small cell sarcomas'
Irinotecan	14	0	0	De Angelo	[46]	*n*=7 GIST
9-NC	39	8	25.6	Patel	[47]	Adult sarcoma
9-NC	16	0	6	Patel	[47]	GIST
Exatecan	39	0	46	Pink	[48]	
Vinca alkaloids						
Vinorelbine	14	0	NG	Fidias	[49]	
Thymidylate synthase inhibitor						
Tomudex	22	0	23	Blay	[50]	
Proteasome inhibition						
Bortezomib	15	0	27	Maki	[51]	
P-glycoprotein interacting agents						
Biricodar + doxorubicin	26	35	61	Bramwell	[52]	PFR 3.4 months, inclusion of desmoids
Alkylphosphocholines						
Perifosine (NSC639966)	23	4	15	Bailey	[53]	
VEGF inhibition						
Bevacizumab + doxorubicin	17	12	65	D'Adamo	[54]	
Rafkinase inhibition						
Bay 43-9006	23	13	35	Pacey	[55]	Inclusion of GIST
Multityrosine kinase inhibition						
SU011248 versus best supportive care	207	8	6.3[a]	Demetri	[56]	Limited to refractory GIST
	105	0	1.5			

CR/PR, complete/partial remission; GIST, gastrointestinal stromal tumor; NC, no change/disease stabilization; NG, not given; LMS, leiomyosarcoma; PFR, progression free rate; RD, remission duration; RMS, rhabdomyosarcoma; 9-NC, 9-nitro-20-(S)-camptothecin.
[a]$P<0.00001$ (PFR).

enhanced in patients with relatively moderate hepatic dysfunction without a coincident effect on body clearance. Cotreatment with dexamethasone seems to decrease the incidence of severe toxicity as well as the area under the curve of the drug [59]. Further investigation in sarcomas focuses on combination trials including standard cytostatics such as doxorubicin. A comparative phase III EORTC trial of ET-743 and ifosfamide has been launched in anthracycline-refractory uterine leiomyosarcoma [60].

Preliminary data of a EORTC Soft Tissue and Bone Sarcoma Group (STBSG) trial with brostallicin, another new minor groove binder, revealed two partial responses and in addition 17 patients with disease stabilization at the end of cycle two among 42 included patients [61].

Epothilone B (patupilone derivates)

Epothilone B analogue (BMS-247550), a semisynthetic analogue of the natural product epothilone B, functions as a mitosis inhibitor analogous to paclitaxel (i.e. microtubule stabilization). A total of 31 patients have been treated at a dose of 50 mg/m^2 given as a 1 h-infusion every 3 weeks in a phase II study. A low response rate of 6% was noted accompanied with a considerable toxicity profile (3% death rate because of sepsis, 41% grade II/IV neutropenia, 46% grade III/IV nonhematological toxicities) [32].

Vinca alkaloids

Vinorelbine has been tested in adult-type sarcoma in a single trial showing one complete and three mixed responses in 36 evaluable patients [49]. Vinca alkaloids are part of investigated combination regimens in childhood sarcoma and single-agent activity was demonstrated in RMS [62].

Alkylating agents

Temozolomide

Temozolomide is also an oral alkylating agent, but derived from imidazotetrazine. It exhibits broad-spectrum antitumor activity against murine tumors [63]. It was developed as a potential alternative to dacarbazine [15]. Compared with dacarbazine, temozolomide was found to offer a comparable antitumor activity, good oral bioavailability and a better toxicity profile [64]. 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 [65]. Whereas dacarbazine requires metabolic activation by the liver, temozolomide degrades into MTIC at physiologic pH. Currently used application schedules are either 85 mg/m^2 daily for 21 days or a dosage of 750 mg/m^2 divided in doses over 5 days both on a 28-day cycle. Both regimens resulted in few grade III or IV toxicities. In three studies examining temozolomide for advanced soft-tissue sarcomas an objective response rate of 10% was found. Some more activity was, however, noted in patients with leiomyosarcomas [38,39].

Trofosfamide

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 in a dose 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 before trofosfamide. Three patients responded to treatment [35,36]. 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 leukocytopenia. The daily dose that produced grade II leukocytopenia was 200–250 mg in 65% of the patients. Three patients attained a partial response, all of whom had received trofosfamide as first-line treatment [37]. In all three studies, the toxicity profile was found to be low.

DNA topoisomerase I inhibitors

Irinotecan

Irinotecan has proven activity in SRCT, which might be schedule-dependent. In RMS xenografts, a high inhibition of tumor growth was found when given in protracted low-dose schedules. A retrospective analysis of eight patients with relapse after previous stem cell transplantation salvage chemotherapy consisted of CPT-11 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 RECIST criteria, two partial responses (one RMS and one Ewing sarcoma) were observed [44]. The Children's Oncology Group performed a phase II window trial in pediatric patients with metastatic RMS. A partial response rate of 45% was observed after two cycles (CI 95%, 23–67%) [45]. In 'adult-type' sarcoma patients there is one report available showing no objective response in 14 patients [46]. One half of the patients, however, entered on the trial had a histology of a GI stromal tumors, which restricts the results of this small phase II trial.

Rubitecan (9-nitro-20-(*S*)-camptothecin)

The insoluble compound 9-nitro-20-(*S*)-camptothecin (9-NC), a derivative of the plant alkaloid camptothecin, has been shown to be an inhibitor of topoisomerase I [66]. Initial molecular studies showed that it inhibited DNA synthesis and caused DNA strand breaks. Exposure of U-937 human myeloid leukemia cells to CPT, 9-NC or 9-aminocamptothecin resulted in an 80–100-fold increase in expression of c-*jun* and *jun*-B mRNAs, followed by a characteristic degradation of cellular DNA [67]. 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, 9-NC was found to be highly inhibitory to several human tumors in tissue culture and to xenografts in animals. In a phase I clinical trial, 29 patients with various neoplasms were treated with 9-NC at 1, 1.5 or 2 mg/m^2/day on a 5-day treatment, 2-day rest schedule. The dose-limiting toxicity was hematologic; the next most frequent and significant toxicities were gastrointestinal. In addition, chemical cystitis was observed in 23% of patients. The recommended dose for phase II was 1.5 mg/m^2/day for patients with one pretreatment or no previous therapy [68]. 9-NC was investigated at the MD Anderson during

a two-arm phase II trial. Patients with GI leiomyosarcomas (GIST) comprised one arm and patients with other soft-tissue sarcoma histologies were enroled in the other arm. Fatigue was the most common toxicity, affecting 75% of all patients (20% of all patients had grade 3 fatigue), followed by nausea (66%; 4% of all patients had grade 3 nausea) and diarrhea (64%; 9% of all patients had grade 3 diarrhea). Seven percent of patients required hospitalization for nausea, vomiting and dehydration. Three partial responses were noted among the 39 patients with different soft tissue sarcoma histologies for a response rate of 8% (CI 95%, 0–16%). No objective responses were seen among the 16 evaluable GIST patients. One patient with liver metastases achieved a minor response that lasted less than 8 weeks. Of the 56 patients enroled 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 [47]. On the basis of these and other available data, a formal phase II study of 9-NC in patients with chordomas has been launched by the University of Michigan.

Topotecan

Topotecan as a topoisomerase I inhibitor with its potential activity against tumors with slow proliferation and refractoriness to other drugs [69] was a promising new substance to be evaluated in advanced metastatic sarcoma. The National Cancer Institute of Canada found a 10.3% remission rate (CI 95%, 2.2–27.4%) for topotecan in 29 untreated patients [70]. 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 Southwest Oncology Group performed a phase II trial of topotecan administered as a continuous infusion in adult patients with untreated advanced soft-tissue sarcomas. Topotecan at a dose of 0.5 mg/m^2/day was applied on days 1–21 of repeated 28-day cycles. No objective responses were observed (CI 95%, 0–16%) in 21 eligible patients [41].

Another phase II trial of topotecan in pretreated adult patients revealed no objective remission in 16 patients. Sixty-two percent of the patients had progressive disease at the first response evaluation, whereas only 38% of the patients achieved a disease stabilization lasting for 6 weeks. The calculated progression-free rates at 3 and 6 months were 31.3% (CI 95%, 10.0–52.5%) and 6.3% (CI 95%, 0–18.1%), respectively, and the median overall survival time was 5.5 months (range, 1.5–13.5). On the other hand, topotecan was well tolerated despite severe but uncomplicated neutropenia grade III/IV in 67%. Considering the PFR, topotecan appears to be rather ineffective in pretreated adult soft-tissue sarcoma. Topotecan is currently investigated as addition to standard chemotherapy in pediatric sarcoma patients with unfavorable histology, advanced disease or in the case of relapse [42]. In recurrent or refractory RMS, 10 of 15 pediatric patients attained a response to the combination of cyclophosphamide and topotecan [43].

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-min 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, whereas disease progression was noted in 17 patients (77%) [50].

Liposomal anthracyclines

No formal investigation has been conducted to explore whether patients being refractory to conventional anthracyclines could be effectively treated by liposomal doxorubicin; however, a randomized EORTC STBSG phase II head-to-head comparison of doxil/caelyx versus doxorubicin in untreated patients revealed no advantage in terms of treatment efficacy for the liposomal compound [71].

Combination regimens

Fifty-three of patients with uterine leiomyosarcoma and of leiomyosarcoma at other locations attained a partial response to the combination of gemcitabine and docetaxel. The median time to progression was of 5.6 months [72]. This is an interesting finding, as 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%; CI 95%, 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%), anemia (3.7%), thrombocytopenia (7.4%) and febrile neutropenia (18.5%) [73]. In recurrent or refractory RMS in pediatric patients, cyclophosphamide and topotecan or low-dose metronomic cyclophosphamide with vinorelbine were shown to be active combinations [43,74,75], as well as carboplatin-based salvage regimens such as ICE or CEC for refractory or recurrent Ewing's family tumors or other types of recurrent sarcomas [76,77].

Phase I and ongoing phase II investigations

Bortezomib

PS-341, a proteasome inhibitor, is currently being investigated in a two-arm study in adult patients with metastatic or recurrent sarcomas, including Ewing

sarcoma, osteogenic sarcoma, RMS 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, tumor p53, MDM2, and cyclin D and E expression by immunohistochemistry. Twenty-three patients with different sarcoma histologies have been accrued so far. Toxicity observed includes constipation/abdominal pain, myalgia and persistent neuropathy. Fatigue has been the most common side effect. Of 15 evaluable patients, best response is 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% [51].

Becatecarin

A rebeccamycin analogue with topoisomerase inhibitory properties, NSC 655649, revealed activity during a phase I in a patient refractory soft-tissue sarcoma [78].

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 VX-710 plus doxorubicin in patients with anthracycline-resistant soft-tissue sarcoma, nine of 26 evaluable patients attained responses and seven patients had disease stabilization with a median progression-free interval of 3.4 months [52].

Exatecan

The EORTC STBSG has evaluated the topoisomerase I inhibitor exatecan mesylate in refractory soft-tissue sarcoma. DX-8951f 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 and the final results are negative [48].

Soblitodin

Antitumor activity for TZT-1027, a synthetic tetrapeptide derivative of dolastatin-10 with potent antitumor activity that acts by disrupting cellular microtubule polymerization, was observed in leiomyosarcoma and liposarcoma during former phase I studies. A planned EORTC STBSG phase II investigation with TZT-1027 was, however, stopped before initiation.

Bendamustin hydrochloride

Within the recently founded German AIO soft-tissue and bone sarcoma group bendamustin hydrochloride, a nitrogen mustard chemically related to the alkylating agents chlorambucil and cyclophosphamide, which may also act as a purine analogue owing to a benzimidazole ring, is being investigated in a phase II trial design. Preliminary data revealed some promising efficacy in heavily pretreated adult-type soft-tissue sarcoma [40].

Matrix metalloproteinase

A tetracycline analogue, Col-3 (Metastat), that specifically inhibits the production and activation of matrix metalloproteinase (MMP)-2 and MMP-9 was investigated in a two-stage phase II trial. Phase I data have shown some benefit in pretreated sarcomas and a 44% response rate in KS. Preliminary results of the phase II investigation revealed a 73%-stabilization rate beyond week 8 [79].

Alkylphosphocholines

Perifosine (NSC 639966) is a synthetic, substituted heterocyclic alkylphosphocholine that acts primarily at the cell membrane targeting signal transduction pathways. It has been recently documented that the alkylphospholipid perifosine potently also inhibits Akt kinase (protein kinase B) activation. In a multicenter phase II trial 23 patients with refractory soft-tissue sarcomas have received a loading dose of 150 mg orally $\times$ 4 on day 1, followed by 100 mg once daily for days 2–28. One partial response in a myxofibroma was seen, and two patients with myxofibroma and desmoid were progression-free at 6 months (15%; CI 95%, 2–41%). Grade III/IV side effects consisted of gastrointestinal (ileus) and hematological toxicity, fatigue, muscle weakness, pain, and rash. The inclusion of desmoid tumors into such protocols aiming on 6-month progression-free intervals is questionable; however, in spite of the inclusion of low-grade sarcomas the trial failed to reach the success criteria [53].

Epidermal growth factor receptor-1 inhibition

Gefitinib

For the subtype of synovial sarcomas expressing HER-1/epidermal growth factor receptor (EGFR)-1 a phase II study with the EGFR inhibitor Iressa (Gefitinib, ZD1839) has recently started to recruit in different European countries. First results are, however, not encouraging.

Vascular endothelial growth factor (receptor) inhibition

Bevacizumab

Vascular endothelial growth factor (VEGF or vascular permeability factor) is an important angiogenic factor that is upregulated in numerous benign and malignant disorders, including angiosarcoma, hemangiomas and solid tumors [80]. Whether this observation is helpful to be adapted in newer treatment strategies is unclear. A phase II trial of doxorubicin combined with bevacizumab has been conducted in 17 patients with metastatic disease [54]. Response rate was 12% and 65% of patients were stable for ≥ 4 cycles. Six patients developed cardiac toxicity grade ≥ 2, two of whom at a doxorubicin dose $< 400\,mg/m^2$. A single patient died of recurrent bilateral pneumothoraces, possibly treatment-related.

Platelet-derived growth factor receptor-β inhibition

Imatinib mesylate

Recent studies have determined the molecular identity of 'classical' dermatofibrosarcoma protuberans (DFSP), giant cell fibroblastoma, Bednar tumor, adult superficial fibrosarcoma, and the granular cell variant of DFSP [81]. DFSP is typically associated with a translocation between chromosomes 17 and 22, which places the platelet-derived growth factor-B (PDGFB) under the control of the collagen 1A1 promoter. In approximately 8% of DFSP cases, the COL1A1–PDGFB fusion is, however, not found, suggesting that genes other than COL1A1 or PDGFB might be involved in a subset of cases. A trial in eight patients with locally advanced DFSP, who had evidence of t(17;22), demonstrated a clinical response to imatinib at 400 mg twice daily (including four complete response). In contrast, patients without t(17;22) had no clinical response to imatinib [82]. Imatinib is an active agent in the treatment of advanced aggressive fibromatosis. Imatinib response in aggressive fibromatosis patients may be mediated by inhibition of PDGFRB kinase activity [83].

For chordoma no effective medical treatment is currently established. A recently published article reported six patients with PDGFRB-positive tumors (and/or phosphorylated PDGFRB, $n = 4$) who have been treated with imatinib mesylate at a dosage of 800 mg daily. After a long treatment period of 1 year tumor liquefaction was evident. In four of five symptomatic patients, a subjective improvement was observed earlier in the course of treatment. Activity was suspected to be mediated by inactivation of PDGFRB [84].

The activation of the PDGF and c-kit receptors has been proposed as important in mediating the growth of AIDS-related KS. In 10 patients with AIDS-related cutaneous KS, which progressed despite chemotherapy and/or highly active antiretroviral therapy, five patients attained a partial response. Biopsies after 4 weeks of therapy demonstrated histologic regression in four of six patients [85]. Patients with other sarcoma subtypes unselected for a molecular target are unlikely to benefit from imatinib mesylate [86].

Raf kinase inhibition

Bay 43–9006, a orally active Raf kinase and VEGFR inhibitor, was investigated in a multicenter, placebo-controlled, randomized discontinuation phase II trial (400 mg twice daily for 12 weeks). To date 27 patients with advanced sarcoma including GIST have been entered and 23 patients are available for response. At 12-week assessment three patients responded (two GIST, one synovial sarcoma) and five patients had a disease stabilization [55].

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.

Mammalian target of rapamycin serine/threonine kinase inhibitor

Mammalian target of rapamycin serine/threonine kinase inhibitor (Everolimus, RAD001) is being investigated in combination with imatinib to define the maximum tolerated dose in refractory GIST. A phase II trial will be launched at the end of 2005 [87].

Protein kinase C inhibitors

Protein kinase C inhibitor (PKC412) inhibits VEGF, PDGF, c-kit and FLT3, as well as the conventional PKC isoforms (a, b, g). A strong drug–drug interaction was found in a phase I trial when combined to imatinib in a dosage of 600–1000 mg/day and PKC412 100–200 mg/day [88].

Other multityrosine kinase inhibitors

Multityrosine kinase inhibitor SU011248 (sunitinib malate), is a multifunctional tyrosine kinase inhibitor of c-kit, VEGFR and FLT3. In a randomized phase III trial comparing sunitinib versus best supportive care in imatinib-refractory GIST, a highly significant difference in progression-free (1.5 versus 6.3 months) and overall survival was found [56]. AMG706, also a multifunctional tyrosine kinase inhibitor of c-kit, PDGFR and VEGFR, has been investigated in phase II trial. More than 130 patients have been included and first results are expected to be available in mid 2006. Other phase I trials started with ANN107, perifosine, each in combination with imatinib and with BMS-354825, an inhibitor of PDGFRA, src and bcrabl.

Other therapeutics being developed in soft-tissue sarcoma are HSPPC-96, a heat shock protein vaccine, and GPX-100, a noncardiotoxic analogue of doxorubicin. Anti-bcl-2 antisense studies are also planned in different sarcoma subtypes, preferentially in chondrosarcoma with known high bcl-2 expression.

Vaccines and cellular targeting approaches, such as MAGE-12 peptide vaccine, tumor-specific peptide vaccination + interleukin-2 or heat shock protein peptide vaccine, are also being investigated in many centers. Intravenous injection of antineoplastons, A10 and AS2-1, which are naturally occurring peptides and amino acid derivatives that control neoplastic growth by arresting the cell cycle in the G_1 phase and by reducing mitosis, have been used in rare cases; however, efficacy is not proven. Glitazones, PPAR receptor-γ ligand are currently investigated in low-grade-(G1) liposarcoma. Dosage of the drugs is, however, discussed controversially [89]. The

cyclin-dependent kinase inhibitor flavopiridol is also part of trials in soft-tissue sarcoma [90].

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), tumor 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 [91].

Conclusions

The treatment of refractory sarcoma is complex. Limited agents are available and standard drugs in patients with anthracycline-refractory soft-tissue sarcomas are associated with significant toxicity. SRCTs (Ewing/PNET, desmoplastic SRCT, RMS), 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 topoisomerase I poisons. In relapsed 'adult' soft-tissue sarcomas trofosfamide appears to be a drug associated with some activity and a considerably low toxicity profile. It produces remissions and disease stabilizations even in patients pretreated with ifosfamide. Gemcitabine has also activity, particularly in patients with non-GI leiomyosarcoma, angiosarcoma and malignant fibrous histiocytoma. The data on prolonged gemcitabine infusions suggest improved activity based on prolonged intracellular gemcitabine levels. Ecteinascidin-743 has been one of the most extensively tested agents, and its ability to slow growth kinetics of a tumor and stabilize 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. Paclitaxel induces high response rates in specific vascular sarcomas and KS. The role of the newer cytostatic agents (e.g. epothilones, brostallicin) is currently not definable as well as VEGF(R), Raf kinase or drugs which restore sensitivity to P-glycoprotein (MDR-1), anti-bcl-2 antisense molecule, cyclin-dependent kinase inhibitors, or mammalian target of rapamycin inhibitor, which continue to be tested in GIST patients refractory to imatinib mesylate 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 EGFR-1 in synovial sarcoma with gefitinib or PDGFRB inhibition with imatinib mesylate in DFSP or as suggested in chordoma and KS. Owing to the paucity of effective agents, consideration of clinical trial participation for patients with relapsed or progressing disease is appropriate.

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