Update on clinical research and state of the art management of patients with advanced sarcomas and GIST

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ABSTRACT

Sarcomas constitute a rare group of malignancies. According to histology, different treatment options are effective. For gastrointestinal stromal tumours (GISTS), targeted treatment with imatinib controls about 20% of advanced or metastatic disease, whereas chemotherapy is more effective for the rest of the sarcomas. Currently, new targeted treatments are emerging, showing activity in cases resistant to established primary treatment. On the other hand, the exciting results of immunotherapy for other solid tumours, for example, melanoma and lung cancer, make it a promising option in the fight against sarcomas. In this review, we have collected data of established and promising treatments in trials with a view to facilitating the sequencing of sarcoma treatments and for identifying the future of these therapeutic options.

INTRODUCTION

In recent years, we witnessed the advent of a new era in the treatment of systemic disease in oncology; immunotherapies seem to be the new hype in advanced malignant melanoma, lung and other types of cancer, whereas chemotherapy and targeted therapies re-emerge for other malignancies such as prostate cancer. Sarcomas represent a rather rare entity, classified into numerous subgroups according to the tissue of origin.1 Still the treatment of systemic disease follows the ‘cornerstones’ of modern medical oncology—chemotherapy and targeted therapies. The scope of this review is to provide an update on the optimal management of patients with advanced sarcoma, and highlight the recent advances that could lead to a change in medical practice in the near future.

PART A: UPDATE ON GASTROINTESTINAL STROMAL TUMOURS (GISTS)

GISTS represent the commonest type of sarcoma.2 While small GISTS (smaller than 1 cm) are quite frequent in the general population among those over 50 years of age and show little or no malignant potential, larger tumours are rare—with an incidence of about 1/100 000. Approximately 40% of patients with larger tumours will eventually develop metastases after macroscopically complete surgical resection, the primary choice of treatment for GISTS.3 There are two interesting points in GIST biology—first, ‘classic’ chemotherapy has minimal influence on GIST cells, with patients suffering from metastatic disease having, until recently, a dismal prognosis.4–7 Second, the survival of the tumour cells depends in about 90–95% of the cases on activating mutations of the genes encoding KIT or platelet-derived growth factorα (PDGFR-α) receptor.8 These mutations are located in 70% of the cases in KIT exon 11, 10% in KIT exon 9 and about 10% in PDGFR-α exons 12 or 18.9 The remaining 10% are considered to be ‘wild-type’ GIST, although the term ‘non-KIT non-PDGFR mutated’ is more suitable as more and more mutations are being identified in other genetic loci.10

Imatinib and KIT-mutated GIST

Imatinib was first tested in patients with metastatic GIST at several dosages, ranging from 400 to 800 mg daily, until a large phase III trial established 400 mg daily as the standard dose.12 This study which randomised 746 patients in only 9 months to receive either 400 or 800 mg imatinib daily showed that median overall survival (OS), progression-free survival (PFS), or response rate (RR) did not significantly differ between the two arms, whereas >3 grade toxicity was higher in the 800 mg arm. Demetri et al13 reported the 10-year follow-up data of this study at the American Society of Clinical Oncology.
(ASCO) meeting of 2014. The authors showed a median OS of 52 months with 22% of the patients being alive after 10 years. There was no difference in the 10-year survival between the two arms. Interestingly, 49% of these ‘long-term survivors’ had been treated with imatinib alone; the rest had received additional systemic treatment such as sunitinib and sorafenib, and metastasectomy or radiotherapy. Demetri et al further showed that patients with an exon 9 mutation had a significantly worse median OS than the ones with exon 11 mutations (38 vs 66 months, p=0.001); this was also depicted by the absolute numbers of the patients being alive after 10 years (32 vs 262). In the paper by Blanke et al, about one-third of the patients who had progressed on 400 mg imatinib and received 800 mg subsequently showed a further stabilisation of their disease. However, as noted, this led to no difference in the 10-year survival. This phenomenon could be explained through the additional therapies applied in each arm, but further factors affecting survival in patients with GIST (such as mutational status, size and localisation of tumour and mitotic index) could also have played a role. To conclude, imatinib in metastatic GIST can convert a lethal disease into a chronic one in roughly 20% of cases. Despite this, the question remains on how to treat the 80% of KIT-mutated patients who subsequently develop resistance to imatinib, as well as those patients who are not KIT-mutated.

PDGFR-α mutated GISTs

PDGFR-α mutations in KIT wild-type GISTs have been first described in 2003. It has been shown that PDGFR and KIT mutations were mutually exclusive, and that GIST cells with PDGFR-α mutation were no different with regard to signalling cascades and progression potential as the KIT-mutated cells. As a result, these patients have been treated with imatinib as well. Cassier et al published in 2012 the latest largest analysis of imatinib efficacy in this patient population. The authors evaluated 57 patients and showed an overall RR of 18% with a PFS of 6.4 months; there was no difference according to imatinib dose (400 or 800 mg). However, not all PDGFR-α described mutations showed the same response to imatinib: in the subset of patients (N=32) with the PDGFR-A-D842V genotype, the RR dropped down to zero and PFS measured only 2.8 months. This finding was in concordance with previous studies which tested the in vitro sensitivity of PDGFR-α mutated GIST cells to imatinib and this led to the development of D842V-specific inhibitors. One of these inhibitors, crenolanib, has already shown promising activity in vitro and is now being tested in a phase II trial. The results of this study are eagerly awaited and will be available within the next few months.

Progressive KIT-mutated GISTs

Sunitinib

Gramza et al elegantly reviewed the mechanisms through which GIST cells are either inherently resistant on imatinib or become resistant to this treatment. Inherently resistant are mostly the cells with specific mutations (as the PDGFR-A-D842V) or with activation of other signalling cascades (as the ones with BRAF/RAS mutations or insulin-like growth factor 1 receptor (IGF1-R) expression). The most common explanation for resistance development is the selection of clones with secondary KIT or PDGFRA mutations. Based on these findings, further TKIs have been tested in imatinib-resistant/intolerant GISTs. Among these, sunitinib has already established its role after a large phase III study showed that patients on sunitinib (compared with the ones having been treated with placebo) had a longer median time to progression (TTP), but not OS. Interestingly, in this study, patients with exon 9 mutations had a better outcome than those with exon 11 mutations (TTP 19 vs only 5 months). Recently Reichardt et al have reported their results of a large ‘real-life’ sunitinib study in imatinib-resistant or intolerant GIST patients. They analysed a total of 1124 patients, the largest cohort in sarcoma studies ever. Owing to the concept of this trial, the dose of sunitinib was somehow ‘liberal’: 599 patients had been treated with the initial dose schedule of 50 mg daily for 4 weeks in a 6-week cycle, and 525 had either started on the 37.5 mg continuous dosing or had received sunitinib in an individually adjusted dose (eg, due to intolerance). The median TTP for the entire cohort was 8.3 months, and the median OS 16.6 months. The objective RR was (only) 8%, but 60% showed disease stabilisation. A post hoc analysis showed that TTP for the patients receiving ‘standard’ sunitinib (50 mg) was only 5.2 versus 12.7 months for those taking the ‘alternative’ dosing. This could be partly explained by the side effect profile of these dose schedules, as 34% of the ‘standard’ patients (26% in the ‘alternative’ group) discontinued treatment due to adverse effects. In other words, effectively adjusting sunitinib dosing enabled these patients to be treated for a longer time. However, and in accordance to the conclusion of the authors, there are no prospective data to further support this post hoc analysis, and therefore, this is merely ‘hypothesis-generating’.

Regorafenib

Regorafenib is a multi-TKI that is active against several protein kinases responsible for angiogenesis, tumour growth, and regulation of microenvironment. It has been first tested in patients with GIST in a phase I, and thereafter in a phase II trial where it proved itself safe with promising activity until a large phase III study established its role in this setting as a further therapy option for patients with GIST progressing after imatinib and sunitinib treatment. In this study, 199 patients were randomised 2:1 to receive either 160 mg regorafenib daily (3 weeks on treatment followed by 1 week off) or placebo. After progression and unmasking of treatment, almost every placebo patient (85%) received regorafenib. The primary end point of the trial was PFS, and this
amounted to 4.8 months in the regorafenib arm versus 0.9 months in the placebo arm. OS did not differ between the two groups (HR 0.77, \( p=0.199 \)), possibly due to the high percentage of crossover. Regarding toxicity, adverse events of any grade occurred almost universally with regorafenib (98% vs 68% with placebo) and grade \( \geq 3 \) toxicity was observed in 61% and 14% of the patients, respectively. This has led to a dose reduction in 72% of the regorafenib cases, generating uncertainty about the appropriateness of the starting dose. Recent work suggests\(^2^3\) that the crucial point in regorafenib-therapy is dose individualisation leading to better patient compliance and thus, increased possibility of health benefit.

**Sorafenib**

Activity of sorafenib (a multikinase inhibitor against KIT, VEGFR, PDGFR and other tyrosine kinases) has been evaluated by Montemurro \textit{et al}\(^2^5\) in a retrospective analysis of 124 patients with GIST who had progressed on imatinib and sunitinib. After a median follow-up of 7.9 months, 60% of patients had achieved stable disease (SD) and an additional 10%, a partial response (PR). In accordance to the other TKIs, the tolerability of sorafenib was only moderate (skin toxicity, fatigue, and diarrhoea being the most common side effects), and dose individualisation led to better compliance of the patients with a trend towards better outcome (PFS 7.5 vs 5 months, HR 0.69; \( p=0.15 \) for dose adjustment vs not).

**Ponatinib**

A further TKI with promising activity in GIST pretreated patients is ponatinib. This molecule was first tested in vitro as well as in mouse models against imatinib, sunitinib, and regorafenib,\(^2^6\) and it showed increased activity against a plethora of KIT primary and secondary resistance mutations. Based on these results, ponatinib is tested in a phase II trial, where patients—progressing on imatinib, sunitinib and regorafenib—receive 45mg of ponatinib. The patients are stratified according to the presence or absence of exon 11 mutation; the first results were presented in ASCO 2014 and updated in the European Society for Medical Oncology Congress (ESMO) 2014.\(^2^7\) Patients with exon 11 mutations showed an overall response of 9%, but the ‘clinical benefit rate’ (CBR) at 16 weeks, which was the primary end point of the study, reached 50%. On the other hand, patients with no exon 11 mutations profited only modestly. The study is expected to be completed in May 2016, but these first results already point to ponatinib being another option for heavily pretreated patients, especially those with exon 11 mutation. However, the toxicity profile represents a major concern for this treatment, as up to 9% of patients receiving ponatinib for other indications, such as chronic myeloid leukaemia, developed serious arterial thrombosis.\(^2^8\)

**Nilotinib**

Nilotinib is another TKI with promising activity in imatinib-resistant GIST patients, and this is mostly due to its ability to inhibit in vitro certain mutations of KIT that are imatinib-resistant. It has been tested in a phase III trial versus best supportive care in patients progressing or intolerant to imatinib and sunitinib, and showed a longer PFS in the intent-to-treat (ITT) population (119 vs 70 days; \( p=0.0007 \)), as well as a trend for a better OS (332 vs 280 days; \( p=0.29 \)).\(^2^9\) Based on these results, the molecule was then tested as a first-line treatment head-to-head against imatinib in a large phase III trial.\(^3^0\)

Owing to crossing the futility boundary in a preplanned interim analysis, the trial stopped recruiting at 647 patients instead of the preplanned 736. Patients were randomised 1:1 to receive either 400 mg nilotinib daily or 400 mg imatinib. 24% of the nilotinib patients versus only 14% in the imatinib group had progressed at the time of the analysis (HR 2.03), and 17 patients (vs 7) had died under nilotinib (HR for death: 2.66). Objective response was also higher with imatinib than with nilotinib. Thus, nilotinib cannot be recommended as a first-line therapy, but may potentially constitute an option for salvage therapy.

‘**Wild-type**’ GISTs

**Linsitinib**

‘Wild-type’ GISTs often overexpress the IGF1-R,\(^3^1\) an observation that has led to the development of the respective inhibitors. Linsitinib is a TKI with in vitro efficacy against IGF1-R, which has been already tested in a phase II trial in patients with wild-type GIST. The first results of the study, based on the analysis of 20 treated patients, have been presented at ASCO 2014.\(^3^2\) The authors could show that the CBR (defined as the sum of complete response (CR) PR and SD≥9 months) was 45%, and the estimated PFS and OS at 9 months measured 52% and 80%, respectively. Grade \( \geq 3 \) toxicity was reported in <10% of the patients with the most common side effects being fatigue, nausea, and transaminase elevation. The study is now completed and the final results are expected.

**TKIs in GIST**

All currently available TKIs have replaced chemotherapy in the treatment of GIST, as the latter seems to have no major impact on the course of the disease. Imatinib is and probably will remain the first choice of therapy for KIT-mutated GISTs as it is highly effective, and the head-to-head comparison with newer TKIs (eg, nilotinib) in the first-line setting resulted in its clear superiority. On progression, treatment with sunitinib and in third line regorafenib are the treatment of choice. For PDGFR—a mutated GIST imatinib remains an acceptable option. On positive results from the ongoing phase II trial with crenolanib, this molecule could be considered for D842V-mutated patients. ‘Wild-type’ GISTs still
pose a difficult clinical problem; therefore, clinical studies solely in this setting (eg, with a specific inhibitor, such as fnsitinitib) are eagerly awaited.

However, the most important lesson comes from the dosing schedule. Thus, it is preferable to freely adjust the recommended TKI-dose to the patient’s needs and side effects, aiming at longer treatment periods instead of tenaciously striving on full dosage that could lead to long delays and permanent discontinuation of therapy, with a negative impact on PFS and survival.

PART B: UPDATE ON OTHER SARCOMAS
First-line treatment: chemotherapy combinations versus monotherapies
Doxorubicin and ifosfamide alone or in combination
One of the most active chemotherapeutics in sarcomas is doxorubicin, which was first tested as a monotherapy in the remote “70s.33 Over the years, other compounds were tested and ifosfamide particularly showed a substantial RR in pretreated sarcomas.34 The next logical step was to combine these two substances. Indeed, at least two preliminary studies showed that the combination of doxorubicin and ifosfamide was active.35 36

In the phase II study of Leyvraz et al,36 female patients with advanced or metastatic gynaecological sarcomas received 75 mg/m² doxorubicin divided into three bolus doses over 3 days together with 10 g/m² ifosfamide as a continuous infusion over 5 days. The authors could show an overall RR of 49%, and concluded that this regimen represented an effective treatment option.

However, until recently, the doxorubicin-ifosfamide combination was not tested in a large phase III study as a first-line treatment option. In 2014, Judson and colleagues published their phase III randomised controlled trial of 455 patients with high-grade, locally advanced and unresectable or metastatic sarcoma who had been randomly assigned 1:1 to receive either doxorubicin and ifosfamide 10 g/m² randomly assigned 1:1 to receive either doxorubicin and ifosfamide 10 g/m² over 4 days.37 Primary end point was OS which was not significantly different between the two arms: 12.8 months in the doxorubicin versus 14.3 months in the combination group (HR 0.83, p=0.076). Median PFS favoured the combination arm with an absolute difference of 2.8 months (7.4 vs 4.6 months, p=0.003); this was also the case for best overall response: 26% of the patients responded with doxorubicin plus ifosfamide 10 g/m² versus only 14% with monotherapy (p=0.0006).

Nevertheless, this benefit came at a price of increased toxicity as more patients in the combination arm experienced grade 3–4 side effects, particularly cytopenia, febrile neutropenia, and nausea/vomiting. Thus the authors concluded that the combination of doxorubicin and ifosfamide should be reserved for cases where high response is urgently needed, for example, for symptom control or where critical structures are endangered. Otherwise, sequence of therapy lines with doxorubicin and ifosfamide-monotherapy should be preferred.

Gemcitabine-docetaxel versus doxorubicin
Apart from doxorubicin and ifosfamide, numerous other chemotherapeutics have been evaluated for treatment of sarcomas, either as monotherapy or in combination.38 39 Regarding combination therapies, most promising seemed the addition of gemcitabine to docetaxel, as a retrospective analysis as well as a prospective phase II study after first-line chemotherapy showed a RR of up to 24% and a PFS of nearly 18 months.40 41 Whether this combination could compare favourably against standard doxorubicin in the first-line therapy was the question of the GeDDIS trial. The primary end point was set on PFS rate at 6 months, and 257 chemotherapy-naive patients with locally advanced or metastatic sarcoma were randomised to receive either doxorubicin or gemcitabine-docetaxel. The results of this study were first presented at ASCO 2015 by Seddon et al.42 An equal median PFS (5.4 months for doxorubicin vs 5.5 months for gemcitabine-docetaxel) as well as a similar percentage of PFS at 24 weeks between the two arms (46.1% vs 46% PFS at 24 weeks) were shown. However, the unadjusted HR for PFS clearly favoured doxorubicin by slightly missing statistical significance (HR: 1.28, p=0.07). More patients went off study due to unacceptable toxicity in the combination arm (16% vs 2%) and clearly less patients required a dose reduction of doxorubicin compared with gemcitabine-docetaxel with the mean dose intensity of 95% and 83%, respectively. The emergence of grade 3–4 side effects was not statistically significant between the two arms, but still slightly more prominent in the combination arm (64.8% vs 71.4%). The authors concluded that due to lack of benefit in terms of PFS, the calculated HR, and the side effect profile, doxorubicin should remain the standard first-line treatment for advanced/metastatic sarcomas.

Doxorubicin monotherapy should remain the standard first-line treatment for sarcoma as long as a fast and high response is not an absolute necessity. Ifosfamide could represent a meaningful second-line therapy, whereas combination therapies beyond first line should be used with extreme caution and after consideration of the medical needs of the patient.

Postprogression treatment: novel therapies
Yet, an important question is whether ifosfamide should be considered as a standard postprogression treatment as an increasing number of options are becoming available.

Trabectedin
Trabectedin is a marine-derived alkaloid which showed a minimal RR in a phase II study on metastatic non-GIST sarcomas that had progressed after one or more lines of chemotherapy.43 However, the rate of ‘progression arrest’, the sum of PR and SD were up to 56%. The high percentage of response was mainly seen in the subgroup of leiomyosarcomas, leading Demetri et al to conduct a phase II study with trabectedin solely in post-first-line
recurrent metastatic liposarcoma or leiomyosarcoma. Median TTP was 3.7 months with a three-weekly regime of trabectedin. The progression-free rate at 3 and 6 months was 53% and 57%, respectively, and was favourably comparable to historical data. A recent trial tested six cycles of trabectedin versus continuation until progression. A significant difference in PFS at 6 months was observed (51.9% vs 23.1%, p=0.02 in favour of maintenance). In all studies, the toxicity profile of trabectedin was well manageable and consisted primarily of increase in liver enzymes, neutropenia, and fatigue.

Trabectedin is currently tested in a large phase III study as second-line treatment in metastatic leiomyosarcoma and liposarcoma. A total of 495 patients have been randomised 2:1 to receive either trabectedin or dacarbazine. Primary end point is OS and secondary end points are PFS, overall RR, duration of response, and safety. An interim analysis was presented by Demetri et al at ASCO 2015. The median OS was similar between the two arms (12.4 vs 12.9 months, respectively), but median PFS was significantly longer in the trabectedin arm (4.2 vs 1.5 months, p<0.0001). The observed benefit was equal in both leiomyosarcoma and liposarcomas subgroups. Demetri et al could also show an improved ‘clinical benefit rate’ from trabectedin (CR, PR, SD×18 weeks) of 34.2% versus 18.5% (dacarbazine). Another interesting finding was a significantly prolonged time to a subsequent treatment in the trabectedin arm (6.9 vs 3.7 months, p<0.0001). However, the observed toxicity was clearly higher with trabectedin, as 64.7% of the patients experienced grade 3–4 drug-related adverse events (vs 36.8% with dacarbazine), which consisted mostly of neutropenia, liver enzyme increase, and nausea. Although this interim analysis could not show an OS benefit, the improved PFS and the shown CBR makes trabectedin a promising second-line option despite its toxicity profile. Final results are awaited.

Aldoxorubicin

In the second-line setting and beyond, another novel drug—aldoxorubicin—was brought into focus after a phase Ib/II trial showed a PR in 20% and SD in 40% of the patients. Aldoxorubicin is a combination of doxorubicin with a linker, which has the ability to covalently bind to albumin when the drug is infused into the blood stream. When the drug reaches the acidic tumour environment, the decrease of the pH ‘releases’ the linker, thus achieving a much higher doxorubicin concentration in the tumour itself. In this first study, a total of 25 patients were enrolled and 17 of these patients had metastatic sarcoma, with all patients having progressed after at least one line of chemotherapy. The maximum tolerated dose was established at 350 mg/m² which—according to the authors—is equivalent to the delivery of 260 mg/m² doxorubicin per chemotherapy cycle. The most common side effects included pancytopenia, nausea, fatigue, alopecia, but not cardiac toxicity. Within the sarcoma subgroup, 38% of these patients achieved a PR with a further 46% remaining stable.

On the basis of these results, a phase IIb trial was conducted which compared head-to-head aldoxorubicin with doxorubicin in the first line treatment of patients suffering from advanced sarcomas. The first results were presented by Chawla et al in ASCO 2014. For the treatment, 123 patients with advanced sarcoma were randomised 2:1 to receive 350 mg/m² aldoxorubicin or the standard dose of 75 mg/m² doxorubicin. Median PFS was significantly longer in the aldoxorubicin arm (8.4 vs 4.4 months, p=0.0002), and so was the overall RR (24% vs 53%). More patients with aldoxorubicin experienced grade 3–4 neutropenia (28% vs 15%), nausea (10% vs 0%), and fatigue (5% vs 0%); however, <50% decrease in left ventricular ejection fraction was more common with doxorubicin (9.5% vs 0%).

Although the latter study has not been as yet published in a peer-reviewed journal, all these data make aldoxorubicin a promising new sarcoma treatment. The molecule is now being tested as a second-line monotherapy versus physician’s choice in a large phase III trial as well as a palliative treatment in combination with ifosfamide in a phase I/II trial. These studies will further help to clarify whether aldoxorubicin will establish its role in the therapeutic armamentarium against sarcoma.

Eribulin

Eribulin is an inhibitor of microtubule-dynamic that is active in metastatic breast cancer. Preliminary results pointed to a meaningful clinical activity in patients with sarcoma, and this led to a randomised phase III trial of eribulin versus dacarbazine in the third-line therapy setting of patients suffering from advanced liposarcoma or leiomyosarcoma. This trial randomised on a 1:1 basis 452 patients, and showed that the primary end point of OS was significantly increased in favour of eribulin (13.5 vs 11.5 months, p=0.0109). However, PFS did not differ between the two groups, being 2.6 months. There have been reported two grade 5, possibly treatment-related events, in the eribulin arm versus none in the dacarbazine group; in total, there was a higher incidence of more than grade 3 side effects with eribulin (67% vs 56%).

There are two interesting points in this trial. First, this is one of the very few sarcoma studies showing benefit in OS. More interestingly, this benefit emerged despite lack of difference in PFS. This ‘discrepancy’ has been observed also in trials with eribulin in metastatic breast cancer, and could be explained through the effect that eribulin has on the tumour microenvironment and vascularisation. However, in the sarcoma trial aforementioned, more patients in the eribulin arm received dacarbazine postprogression as vice versa. Although the authors stated that this difference was not strong enough to explain the OS difference, still it could have influenced the trial results. Second, severe side effects were not significantly higher in the eribulin (67%) compared with dacarbazine.
with the dacarbazine arm. Quality of life (QoL) did not significantly differ between the two arms; however, as QoL was only an exploratory end point of the trial, the question still remains whether such a high percentage is acceptable in a heavily pretreated population in the third-line setting.

Pazopanib

Pazopanib is a multi-TKI and has been first tested in a phase II study of patients with advanced sarcoma who have failed or were not able to receive standard first-line chemotherapy. In this trial, the progression-free rate at 3 months (being the primary end point of the study) was up to 49% for leiomyosarcomas. The toxicity profile was well manageable and consisted mostly of hyperbilirubinaemia, hypertension, and fatigue—all of which were observed in <10% of the patients. Pazopanib was then tested in a large randomised, placebo-controlled phase III trial (PALETTE) of 369 patients with advanced sarcoma who had failed at least one line of chemotherapy. Median PFS significantly favoured pazopanib with 4.6 versus 1.6 months in the placebo group (p<0.0001), but OS had not reached statistical significance (12.5 vs 10.7 months). The authors explained this through the longer OS observed with placebo as well as through the postprogression therapies given that might have influenced the final OS rate.

An interesting outcome of this trial has recently been published by Coens et al. The authors reported on health-related quality of life (HRQoL) of the PALETTE-treated patients having been an exploratory end point of the trial. The patients had to fill out the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (EORTC QLQ-C30) at baseline and at weeks 4, 8, and 12 after starting treatment. The analysis showed a similar score between the two arms, both at the beginning of the study as well as at the prespecified time points. Global health status in the pazopanib arm did drop by 3.8 points at week 4, but this was not clinically significant. Patients in the pazopanib arm also reported increased rate of diarrhoea, loss of appetite, nausea/vomiting, and fatigue which correlates with the known side effect spectrum of this treatment, but this did not translate into a significant worsening of the global health status in general. Thus the authors concluded that increasing PFS (as shown in the PALETTE study) without significantly affecting general QoL makes pazopanib an acceptable option for treating patients with progressive sarcomas.

Regorafenib

Given the role of angiogenesis in sarcomas as well as the activity of regorafenib in angiogenesis, this compound was also tested in a randomised, placebo-controlled phase II trial of soft-tissue sarcomas. The first results of this study were presented by Mir et al at ASCO 2015. A total of 55 patients with leiomyosarcoma and 32 with other sarcoma types (mainly undifferentiated pleomorphic sarcomas, angiosarcomas, and fibrosarcomas) were randomised 1:1 to be treated either with regorafenib or with placebo. All of the patients had received at least one line of chemotherapy containing doxorubicin and were not amenable to curative local treatment. The PFS favoured regorafenib in both sarcoma groups (3.7 vs 1.9 months for the leiomyosarcoma group, and 3.7 vs 1.0-month for the other sarcomas). The toxicity profile consisted mainly of fatigue, hypertension, and skin disorders that manifested as grade 3 in about 20% of the patients; however, no grade 4 toxicity was observed. This study is ongoing and further results are expected in the coming months, but already point to a possible role of regorafenib as a second-line therapy in all sarcomas.

HOW SHOULD CHEMOTHERAPIES ‘LINE UP’?

Apart from aldoxorubicin, which was tested in a phase II study against doxorubicin, none of the other therapies tested were tested against doxorubicin or any other broadly used treatment in sarcomas in a large trial. Furthermore, there has been no study comparing the efficacy of one of the modern molecules against another. Thus, it is difficult to propose a rational line up of (chemo) therapy after tumour progression on doxorubicin. In our opinion, this has to be individually decided according to the specific requirements of each patient, the toxicity profile, the subgroup of sarcoma and its molecular biology (e.g. trabectedin and eribulin in leiomyosarcoma and liposarcoma), as well as the cost of each proposed treatment.

GOING INTO THE FUTURE: IS THERE A ROLE FOR IMMUNOTHERAPY IN SARCOMAS?

Immunotherapy constantly gains significance in the fight against cancer as treatment with antibodies against the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1) antigens, both expressed on the T-lymphocytes and serving as ‘brakes’ in our immune system, led to a significant increase in RR, PFS, and OS of melanoma patients (reviewed by Ascierto et al.). Owing to these remarkable results, in addition to a ‘plateau’ of ongoing response in a subgroup of patients, immunotherapy is now tested in a plethora of further tumours such as lung, bladder, kidney, etc. A key player in immunotherapy seems to be the interaction of PD-1 antigen with its ligand PD-L1, as the expression of PD-L1 in the tumour cells was correlated in some, but not all, tumour types with response to anti-PD-1 antibodies. In accordance to these data, Raj et al. reported their analysis of PD-L1 expression in patients with sarcoma. A total of 161 paraffin-embedded osteosarcoma, 33 Ewing sarcoma and 46 leiomyosarcoma samples were analysed with immunohistochemistry for PD-L1 expression, which was found positive in 36%, 39% and 97% samples,
respectively. This result was not correlated with tumour size, grade, age, response to chemotherapy or OS (only osteosarcoma treated with chemotherapy showed a marginally improved OS). In a similar study by Koizak et al., 36 synovial sarcoma samples were analysed (56% primary, 44% lung metastases) and in 83%, PD-L1 expression was revealed and showed no effect on the course of the disease. As it is the case with other tumour types, quantification of PD-L1 expression and its validity are still to be defined. On the other hand, these are interesting exploratory studies that help form the basis to develop trials of immunoimmunotherapy in sarcoma. Thus nivolumab and pembrolizumab, the two most frequently used anti-PD-1 antibodies, as well as the anti-CTLA-4 antibody ipilimumab together with further immunotherapy strategies, such as chimeric antigen receptor T cells, are currently being tested in several phase I–II clinical trials in patients with sarcoma (for a complete overview see also under clinicaltrials.gov). The first results of these studies are expected later in 2016 and until then none of these antibodies can be used for the treatment of patients with sarcoma outside a clinical trial.

NEW PERSPECTIVES, FUTURE DIRECTIONS

In conclusion, the field of sarcomas did not witness a breakthrough in recent years as, for example, melanoma with immunotherapy. Still in GISTs, imatinib can control around 20% of patients; we already have a handful of significantly active treatments in the second-and-beyond line setting. For the other sarcomas, chemotherapy is still the cornerstone of treatment with the newer therapeutic options providing rather marginal benefits. Several interesting studies are expected to be completed within the following years as the view is that immunotherapy will play an important role in the treatment plan of patients with sarcoma. Insights into the molecular biology of the disease are urgently needed for the successful development of personalised targeted therapies.

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REFERENCES

heavily pretreated gastrointestinal stromal tumor (GIST) patients. 


Update on clinical research and state of the art management of patients with advanced sarcomas and GIST

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