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Recent Advances in Advanced Sarcoma Therapy: Medical Oncologist's Perspective

Rastogi S[1]*, Sankhala KK[2] and Chawla SP[2]

[1]*Department of Medical Oncology, AIIMS, India*
[2]*Cancer Center of California and Sarcoma Oncology Center, United States*

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***Corresponding author**

Sameer Rastogi, Department of Medical Oncology, All India Institutes of medical Sciences, India, Email: samdoc_mamc@yahoo.com

Abstract

Sarcomas are extremely heterogenous and exceedingly rare group of malignancies. Broadly, the term 'sarcoma' encompasses both Soft Tissue Sarcoma (STS) including GIST (Gastro Intestinal Stromal Tumors) and bone sarcomas, though there might be some overlap between the two entities. For the years together, the standard treatment for advanced/ metastatic STS was ifosfamide and / or doxorubicin based chemotherapy. Treatment for STS in yesteryears depended largely upon general sensitivity for chemotherapy and not for individual histological subtypes or translocation studies. However, in last few years, with the advent of new agents like imatinib, trabectidin, pazopanib and eribulin, a lot of things have changed. The success in bone sarcomas during this timeframe has not been as tangible as STS but newer therapies like denosumab and Rexin G have some potential activity in selected subsets. In this review, we will try to highlight the latest advances in both advanced/ metastatic STS and bone sarcomas.

Introduction

Sarcomas present with unique challenges in the terms of development of newer therapies because of infrequent occurrence and variegated character. There is outburst of newer therapies in last few years, which have succeeded in advanced soft tissue sarcomas with variable benefits. This is in stark contrast to bone tumors where the treatment has not changed much for advanced stage. Bone sarcomas (namely osteosarcoma and ewings sarcoma) typically in the category of 'few of the potentially curable cancers', when diagnosed early a cure rate up to 90% can be achieved. The challenging area is metastatic bone cancers where lots of work is needed to be done.

Though newer options are available, there is lack of clarity with regards to the optimal use of these therapies including issues like sequencing of the therapies, effect on quality of life and overall survival, histology specificity and use of predictive and prognostic biomarkers. This review will summarize various recent developments that have taken place in last few years for soft tissue as well as bone sarcoma. We would also share a brief thought on the design and end points of future trials in sarcomas.

Pazopanib

Pazopanib is an oral molecular targeted agent which inhibits VEGF, PDGF and other tyrosine kinases. Sleijfer S, et al. conducted a stratified phase 2 trial with pazopanib in patients with relapsed/ metastatic STS and found the Progression Free Survival (PFS) proportion at 3 months was 44% for patients with leiomyosarcoma, 49% for patients with synovial sarcoma, 39% for patients with other types of soft-tissue sarcoma, and 26% for adipocytic sarcoma [1] Based on previously set guidelines for activity in STS (a progression free survival rate of 40% at 3 months) [2] a phase 3 trial was conducted in non adipocytic STS.

Pazopanib for metastatic soft-tissue sarcoma (PALETTE), a randomized, double-blind, placebo-controlled phase 3 trial, randomized 369 patients with non-adipocytic STS to receive pazopanib (n=246) or placebo (n=123) in 2:1 randomization and [3] in this trial crossover was not permitted so as not to confound the effect of subsequent therapies on OS. Regarding previous therapies, majority had received anthracyclines (99%) followed Ifosfamide or analogues (71%), 34% Gemcitabine (34%), Docetaxel (28%), Trabectidin (16%) and Dacarbazine (15%). Median PFS, the primary end point was 4.6 months for Pazopanib compared with 1.6 months for placebo. Overall survival (OS) was 12.5 months (10.6-14.8) with Pazopanib versus 10.7 months (8.7-12.8) with placebo and was not significant. Overall global health and quality of life (qol) scores were not significantly different in between the two arms. Most common grade 3-4 toxicities with pazopanib in this trial were fatigue (13%), hypertension (7%) and diarrhoea (5%).

The positive aspect of this trial was that it was first randomized trial of multikinase inhibitor compared to placebo and broke the dormancy that had crept in the treatment paradigm of STS.

Secondly, this is once a day oral drug and is quite convenient for patients in palliative settings. However, the flip side of this trial was absence of Overall Survival (OS) benefit. Furthermore, the comparison arm was placebo, which is no more standard therapy in the face of so many available chemotherapies.

There is palpable need for the biomarkers guided treatment in sarcoma to delineate the appropriate group of patients benefiting from these therapies. Koehler, et al. in a recently published retrospective study of 19 patients treated with Vascular Endothelial Growth Factor Receptors (VEGFR) inhibition and found that the PFS of patients with TP53 mutations was significantly superior to TP53 wild-type tumors with the median PFS of 208 versus 136 days, respectively [4]. However, this being a small retrospective study is at best hypothesis generating and future research needs to focus on this.

Trabectidin

Trabectidin is a marine derived drug which binds to minor groove of DNA, thus affecting the function of DNA binding proteins and thus causes interference of cell cycle and induction of p53 independent apoptosis. In addition to this, trabectidin also acts on tumor microenvironment and has immunomodulatory and antiangiogenic activity [5].

Trabectidin had shown activity in against STS in various phase 2 trials earlier and the drug was thus given approval in Europe in 2007 for patients with advanced STS who experienced failure of treatment with doxorubicin and ifosfamide [6,7]. In a recently published multicentre trial that subsequently led to FDA approval of trabectidin, 518 patients with leiomyosarcoma and liposarcoma treated previously with anthracycline and one other therapy, were enrolled and randomly assigned to either trabectedin (n =345) or dacarbazine (n =173) in a 2:1 randomization [8]. Trabectidin administration resulted in significant improvement in PFS (median PFS for trabectedin *vs.* dacarbazine, 4.2 *v* 1.5 months; p <0.001), however there was non-statistically significant improvement in OS. Though in preplanned subgroup analysis, the PFS benefit was present in all subgroups but better PFS was seen in myxoid/ round cell group, consistent with previous trials. The most common grade 3-4 toxicities in this trial were neutropenia (37%), thrombocytopenia (17%), anemia (14%) and transaminitis (elevation of either SGOT and/ or SGPT (39%).

This trial had an edge over PALETTE trial, being an active controlled trial however no quality of life assessment was done. Besides, as liposarcoma cases were lesser than leiomyosarcoma and more so for the individual subtype like pleomorphic liposarcoma so the activity in these subtypes further needs to be confirmed.

With proven activity in STS, there is a possibility that if trabectidin used upfront can be better than standard agents like doxorubicin. However, in a recently published phase IIb trial comparing two different schedules of trabectidin and doxorubicin, there was no advantage of trabectidin over doxorubicin in the first line setting though toxicity was higher in trabectidin arm [9].

Eribulin

Eribulin, also known as microtubule dynamics inhibitor is a structural analogue of halichondrin B, originally isolated from the marine sponge *Halichondria okadai*. In addition to being tubule inhibitor it induces vascular remodelling, suppresses migration and invasion of cancer cells, and reverses the epithelial to mesenchymal transition in various cancer cell line. In phase 2 study of soft tissue sarcoma progressed on more than 1 line of treatment, PFS proportion at 12 weeks was 47% for liposarcoma, 32% for leiomyosarcoma and 21% for synovial sarcoma [10].

Taking a cue from its activity in this group Schöffski, et al. conducted a phase 3 trial in patients with intermediate-grade or high-grade advanced liposarcoma or leiomyosarcoma who had received at least two previous systemic regimens for advanced disease (including an anthracycline) [11]. Patients were randomly assigned patients to eribulin (n=228) or dacarbazine (n=224) in this open label multicentric trial. Previous therapies were well balanced between arms and included anthracyclines (85%), gemcitabine (52%), ifosfamide 50%, trabectidin 47%, docetaxel (43%) and other therapies (less than 10%). Overall survival, the primary end point significantly improved in patients assigned to eribulin compared with those assigned to dacarbazine (median 13.5 months *vs.* 11.5 months; hazard ratio 0.77; p=0.0169). However this overall survival could not be attributed to difference in subsequent treatment as subsequent therapies were well balanced between the groups except the higher number of patients in eribulin group received subsequent dacarbazine. Major grade 3-4 side toxicity was asymptomatic neutropenia in 35% of patients. Besides, class effect of microtubule inhibitors, neuropathy occurred in around 20% of patients, majority of them being grade 1 and 2. The preplanned subgroup analysis of this trial revealed benefit only in liposarcoma subgroup, a finding consistent with previously performed phase 2 trial. Based upon this, the U.S. Food and Drug Administration approved eribulin mesylate, for the treatment of unresectable or metastatic liposarcoma for patients who received prior chemotherapy that contained an anthracycline drug (Figure 1).

GIST: A different story of success

Gastrointestinal Stromal Tumors (GIST) is mesenchymal neoplasms related to be arising from interstitial cell of Cajal of myenteric plexus and is typically refractory to the conventional

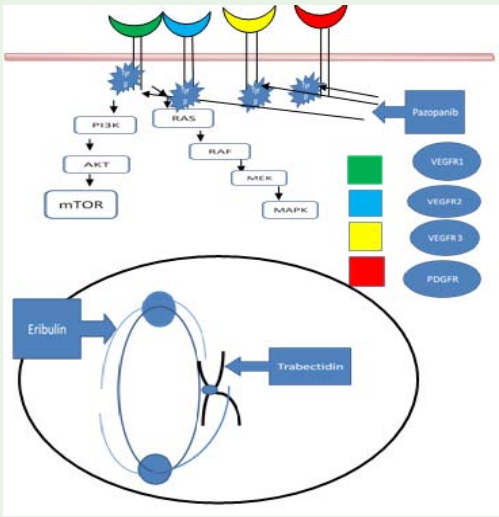

Figure 1: Showing mechanism of action drugs recently approved by FDA for soft tissue sarcoma.

cytotoxic chemotherapy. There are frequent gain-of-function mutations of KIT in GIST resulting in the constitutive activation of KIT signalling, which leads to uncontrolled cell proliferation and resistance to apoptosis. Prior to imatinib era, median duration of survival in patients with metastatic GIST was quite dismal, being 20 months [12]. Imatinib a selective inhibitor of certain protein tyrosine kinases: the intracellular ABL kinase, the chimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, the transmembrane receptor KIT, and the platelet-derived growth factor receptors was tested in GIST with its potential ability to act against kit signal transduction pathway.

Blanke et al. reported long term follow up results of metastatic GIST patients expressing kit, receiving two different doses of imatinib. After a median follow up of 63 months median overall survival was 57 months with objective response rates of 68% [12].

The success of imatinib and relapsing nature of the GIST provided an impetus to the development of second line tyrosine kinase inhibitors. The oral multitargeted RTK inhibitor sunitinib malate targets a number of RTKs, including KIT, PDGFRs-α and -β, and Vascular Endothelial Growth Factor Receptors (VEGFRs)-1, -2, and -3 thus blocking proliferation, survival of GIST cells and inhibiting angiogenesis. In a large, phase 3, multicentre, placebo controlled trial in imatinib resistant/ intolerant GIST patients, sunitinib demonstrated time to progression, TTP (the primary end point) of 26.6 *vs.* 6.4 weeks, significantly higher than placebo [13]. The most common treatment-related non-hematologic grade 3/4 AEs among these patients were fatigue (10%), hypertension (8%), and hand–foot syndrome, asthenia, and diarrhoea (5% each). When sunitinib is used in imatinib failed patients, it is more sensitive in patients with exon 9 mutation and wild type GISTs.

Since all patients with metastatic GIST eventually develop resistance to first and second line therapy, there was active search for third line therapy. Regorafenib is a pan-TKI which inhibits wide range of targets including KIT, RET, RAF1, BRAF, VEGFR1-3, TEK, PDGFR and fibroblast growth factor receptor. In a phase 3 trials in metastatic GIST patients already progressed on imatinib and sunitinib, regorafenib caused significant improvement in PFS, 4.8 months as compared to 0.9 months in placebo arm [14]. The most common adverse events were hypertension, hand foot syndrome and diarrhoea.

Recently, Blay et al. published a phase 3 randomized trial comparing nilotinib versus imatinib in first line in patients with unresectable/ metastatic GIST. Two year progression free survival was significantly better in imatinib as compared to nilotinib, thus at this point of time imatinib remains the best drug for first line therapy in advanced metastatic GIST [15].

Denosumab

Giant Cell Tumor of the Bone (GCTB) is generally benign condition but with unpredictable behaviour in a fraction of patients. RANKL (Receptor Activator of Nuclear Factor Kappa B [NF-kB] Ligand) appears to play an important role in the pathogenesis of GCTB [16]. RANKL is present in stromal cells and activates osteoclasts by virtue of interaction with RANK present on osteoclasts. The developments of new agents like denosumab that target RANKL have opened new avenues for the treatment of this disease, thus preventing giant cell mediated destruction of the bone.

Thomas, et al. performed a single group study of 37 patients with unresectable and/ or recurrent GCTB and treated them with denosumab 120 mg monthly (every 28 days), with loading doses on days 8 and 15 of first month [17]. The primary endpoint was tumour response, defined as elimination of at least 90% of giant cells or no radiological progression of the target lesion up to week 25. Of 35 evaluable patients, 30 (86%) patients had a tumor response. Though formal assessment of pain and quality of life was not a part of this study, of 31 patients for whom data was collected, 26 reported reduced pain or functional improvement.

In the largest phase 2 study till now [18], those patients with surgically unsalvageable GCTB (cohort 1) who could be analyzed (n=169), 96% (163) had no disease progression after median follow-up of 13 months. In patients with salvageable GCTB whose surgery was associated with severe morbidity (cohort 2), after a median follow up of 9.2 months, 74 of 100 (74%) analyzable patients had no surgery while 16 of 26 (62%) patients who had surgery underwent a less morbid procedure than planned. Regarding toxicity profile of denosumab in this study, 1% had osteonecrosis of the jaw and 5% hypocalcaemia. In another study focused on pain and analgesic use in GCTB, interim results suggest pain improvement ≥ 50% of patients in different cohorts at each study visit from months 2-30 [19].

Rexin G

Rexin-G is a targeted gene therapy vector bearing a cytocidal dominant negative cyclin G1 construct. Chawla, et al. reported the combined results of rexin-g tested in a phase I/II study for chemotherapy-resistant sarcomas and phase II study for chemotherapy-resistant osteosarcoma [20]. In phase I/II study, Rexin-G was well-tolerated with no dose-limiting toxicity and exhibited dose-dependent efficacy in terms of tumor control rates, progression-free survival, and overall survival, thus validating both the efficiency of the tumor-targeting technology and the pharmacological mechanisms of action.The efficacy and safety of Rexin G is further reinforced by phase 2 trials reported simultaneously. Of 17 evaluable patients in phase 2 study, 10 patients had stable disease and median PFS was ≥3 months and median OS, 6.9 months. Thus, strongly suggesting its action by the control of tumor growth with a tantalizing possibility of increasing overall survival. In USA, Rexin G received orphan drug status for both soft tissue sarcoma and osteosarcoma in 2008.

Conclusions and Future Directions

There has been unarguable improvement in treatment of advanced STS in last few years with approval of rexin g, pazopanib, trabectidin and eribulin for the abovementioned indications. However, there are few pertinent issues that need to be addressed in future trials. These include the use of prognostic and predictive biomarkers. Besides, cost effectiveness of the newer therapies needs to be established so that these drugs are feasible across the world. Taken further, when the numbers of options have suddenly been around then it is very relevant to know the exact and optimal sequence of these therapies. Since in PALETTE trial, population was treated relatively early in course of the disease it might be prudent to give pazopanib prior to trabectidin in leiomyosarcoma. Furthermore, statistically these trials have been underpowered because the most of these trials have underestimated the survival time in second line setting while calculating sample size.

Further trials also need to explore the issue of quality of life issues properly as it is of primary importance in advanced disease where the benefit of the treatment is at best modest.

Regarding bone sarcomas, the development has been relatively slow. Denosumab is the certainly a ray of hope in this dismal background but there are many question yet to be answered including the effect of denosumab on developing bones, duration of use, appropriate schedule if it needs to be used lifelong, effect on childbearing etc. Need for predictive biomarkers remains a pressing need for this group as well.

Summing up everything, though recent advances have happened in sarcomas but there is still huge gap of knowledge and a lot more needs to be achieved for clinically meaningful benefit in the patients.

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