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Soft tissue sarcomas & GIST

Highlights from ASCO meeting 2016

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Summary Soft tissue sarcomas (STS) are a rare and heterogeneous disease sharing mesenchymal origin. While classification of different STS subtypes has generated insight into their molecular pathogenesis, treatment response, and prognosis, oncological management still poses major clinical challenges. Despite considerable evolution in definition of optimal treatment strategies over the past decade there is a critical need of new and less toxic therapeutic approaches for the treatment of metastatic sarcoma. This review covers the latest clinical study highlights for soft tissue sarcomas and gastroinestinal stromal tumours (GIST) presented at ASCO 2016, demonstrating a constant progress from conventional chemotherapy to histology-tailored therapy as well as immunotherapy approaches.

Keywords Soft tissue sarcoma · GIST · Oncology · ASCO meeting · Immunotherapy

Introduction

Soft tissue sarcomas (STS) are a rare but heterogeneous group of malignant mesenchymal tumors comprising only 1 % of all adult cancers [1]. Historically, successful treatment of sarcoma patients has been challenging and despite initial surgery, distant metastatic disease develops in a quarter of all patients [1]. For the majority of patients with advanced and/or metastatic disease, long-term disease stabilization is the main therapeutic goal [1]. In recent years evidence has been emerging that distinct histopathological differences between sarcoma subtypes can have a significant impact on optimal management [2, 3]. However, standard chemotherapy has been shown to have limited durable effects [1–3] and there is a critical need of novel and less toxic therapeutic approaches for the treatment of metastatic sarcoma.

For tumor types that do not respond to conventional cytotoxic chemotherapy such as gastrointestinal stromal tumours (GIST), research on molecular pathogenesis has provided crucial clues to novel therapeutic strategies [4]. Furthermore, the approval of pazopanib for advanced STS lends some evidence to the possibly important role of vascular endothelial growth factor (VEGF) receptor and related pathways in the growth of different STS subtypes [5]. The most promising approaches in recent decades include immune checkpoint inhibitors, which have reignited enthusiasm for the development of immunotherapy drugs for cancer. By manipulating the immune system, immune checkpoint inhibitors have demonstrated high response rates and prolonged overall survival in selected malignancies [6, 7]. Furthermore the use of immune checkpoint inhibitors alone or in combination with other approaches such as radiation, chemotherapy, targeted agents, or immunotherapeutics has led to further tremendous breakthroughs in cancer treatment [7, 8]. Immunotherapy in the treatment of metastatic sarcomas is still in its infancy. However, based on emerging data from ASCO 2016 there remains optimism that the strides made in other cancers will also be emulated in sarcoma [7].

This review covers the latest clinical study highlights for sarcomas and GIST presented at this year's ASCO meeting, demonstrating the constant progress

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from conventional chemotherapy to histology-tailored therapy and immunotherapy approaches.

STS-TKIs

Tumor angiogenesis plays a key role in the treatment of STS as shown by two clinical studies demonstrating efficacy of multikinase inhibitors in the treatment of metastatic STS:

Nicolas Penel from Lille/France presented the international, randomized, double-blind, placebo-controlled phase II *REGOSARC trial* [9] (abstract 11003) of the French Sarcoma Group and the Sarcoma Platform Austria investigating the activity and safety of regorafenib (RE) in doxorubicin-pretreated metastatic STS. Four independent parallel cohorts of a total of 175 patients with advanced refractory STS (liposarcomas [LPS] $n = 50$, leiomyosarcomas [LMS] $n = 50$, synovial sarcomas [SS] $n = 125$, other sarcomas $n = 50$) were included. For each cohort, patients were randomly assigned 1:1 to receive best supportive care (BSC) plus either RE (160 mg once daily, 3 weeks on, 1 week off) or placebo, with optional crossover for placebo-group patients upon disease progression. Primary end-point was progression free survival (PFS), secondary endpoint overall survival (OS). RE was associated with improved PFS in all cohorts other than LPS. No patient in the study experienced complete response, but in total 4 RE-treated patients had partial responses vs. 0 patients in the placebo groups. RE was generally well tolerated: the most frequent side effects were asthenia, anorexia, diarrhea, mucositis, arterial hypertension, and hand–foot skin reaction. One patient died from acute hepatitis. In conclusion, RE is an active drug providing statistically and clinically significant PFS improvement in pretreated STS patients with comparable effect to pazopanib (PA). However, replacement of PA for RE in adipocytic STS can not be recommended to date.

Data of the *PAPAGEMO trial* [10] (abstract 1104), a multicentric, prospective, phase II study investigating the combination therapy of pazopanib (PA) plus gemcitabine (GEM) vs. PA monotherapy were presented by Hans Joachim Schmoll from Halle/Germany. In total 90 patients with relapsed or refractory STS after at least one anthracycline-based chemotherapy regimen were included. Randomization was stratified by LPS histology and center. The primary endpoint defined as progression rate at 3 months was met with 73.2 % in the combination group vs. 45.5 % in the monotherapy group (hazard ratio [HR] 1.62, confidence interval [CI]: 1.16–2.27, $p = 0.005$). Response rate was 11 % in the combination arm vs. 5 % in monotherapy arm. One patient showed complete and 4 patients partial remission vs. one partial remission under PA monotherapy. Median PFS was 5.6 months vs. 2.0 months, respectively (HR 0.58, $p = 0.006$). Median OS showed no significant difference between the two groups (13.1 vs. 11.2 months, $p = 0.89$). As expected toxicity was aggravated in the combination arm with mainly grade 3/4 hematological, cardiovascular, and GI adverse events. Concluding, based on the relatively small number of patients, combination therapy of GEM/PA cannot be recommended in LPS patients to date.

Sarcomas immunotherapy

Once again immunotherapy remained the highlight of most ASCO presentations—as well as for sarcomas. Furthermore this year was particularly exciting, as the preliminary results of the first clinical trials of checkpoint inhibitors for sarcomas were released:

In the *SARC 028 phase II study* [11] (abstract 1106) 40 patients with high-grade, metastatic STS (leiomyosarcomas [LMS], undifferentiated pleomorphic sarcomas [UPS], dedifferentiated liposarcomas [dLPS], and synovial sarcomas [SS]) and 40 patients with bone sarcomas (osteosarcoma [OS], Ewing sarcoma [ES], and dedifferentiated chondrosarcoma [dCHS]) resistant to at least one prior line of chemotherapy were treated with the anti-PD1 antibody pembrolizumab 200 mg every three weeks until progression. One key interaction between cancer cells and the immune system is mediated by programmed death ligand-1 (PD-L1) and programmed death 1 (PD-1) signaling [12]. PD-1 antibodies such as pembrolizumab inhibit the interaction between PD-1 and its ligands on tumor cells to promote immune-mediated destruction [12]. Overall 11 of the 40 patients with STS and 3 patients with bone sarcomas showed tumor shrinkage. STS patients with tumor shrinkage included 4 patients with UPS, 5 patients with dLPS, and 1 patient with LMS and one with SS each. Responding bone sarcoma patients included one patient with ES, one with OS, and one with dCHS. However, most patients with LMS, SS and ES rapidly progressed. Blood as well as tumor samples were collected of all patients and shall be available with the final results.

In Suzanne George's study [13] from the Dana Farber Cancer Institute in Boston/USA, 12 patients with uterine leiomyosarcoma (uLMS) were treated with nivolumab 3 mg/kg every two weeks. There was no documented tumor response and all patients showed disease progression at the first 3-month scan. According to tumor samples, PD-1 and PD-L1 expression was low or absent while PD-L2 expression was quiet high.

Concluding from the two studies above, data suggests that pembrolizumab may be an active drug especially for patients with UPS or dLPS. As visible from these first data other histological subtypes such as SS, LMS, or ES should be enrolled in clinical trials with combination regimens. Furthermore, identification of adequate radiologic response criteria and corresponding time intervals as well as determining biomarkers predictive of benefit will be essential tasks in the future.

GIST

A phase I/II study presented by von Mehren et al. [14] (abstract 11007) released exiting data about crenolanib (CRE) and its clinical activity in D842V mutant GIST. D842V GIST, a platelet-derived growth factor receptor alpha (PDGFRα) inhibitor with in vitro activity against PDGFRA D842V, is known to be resistant to all available tyrosine kinase inhibitors (TKIs) with a mPFS of ≤2.8 m and a mOS of 14.7 months. In the study, CRE was administered to patients with measurable disease who progressed on a prior TKI at four dosing regimens including 200 mg once daily, 340 mg once daily, 140 mg twice daily, and 72 mg/m^2/three times a day TID. In all, 16 of 20 patients had undergone prior partial [14] or total gastrostomy. Two of 16 patients achieved partial remission (PR) while 3 of 16 showed stable disease (SD); clinical benefit rate was 31 % (5/16 patients). Seven patients stayed on CRE for over 6 months and one patient each for one and two years. Grade 3/4 adverse events (AEs) included reversible elevation of transaminases (3 patients) and anemia (3 patients). One patient each with pre-existing ascites and pleural effusion developed worsening fluid accumulation in the context of disease progression. Despite prior gastrectomy, crenolanib reached a clinically relevant concentration. To date, crenolanib is the first and only TKI showing activity in PDGFRA D842V mutant GIST. A randomized placebo-controlled study of crenolanib in advanced D842V GIST, however, is currently being initiated.

Also for the treatment of GIST, data on immune checkpoint inhibitors were presented by Ronald DeMatteo from the Memorial Sloan Cattering Center in which indoleamine 2,3-dioxygenase (IDO) could serve as a potential immune checkpoint in GIST [15]. IDO is one molecular mechanism that contributes to tumor-induced tolerance: it helps creating a tolerogenic milieu in the tumor and the tumor-draining lymph nodes, both by direct suppression of T cells and enhancement of local Treg-mediated immunosuppression [16]. Furthermore, it can also function as an antagonist to other activators of antitumor immunity. Therefore, strategies to block IDO might enhance the effectiveness of tumor immunotherapy [15, 16]. In vitro DeMatteo could show that imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of IDO. Therefore, combined molecular and immune therapy could improve clinical outcomes in GIST [7, 15, 16].

Sarcoma and GIST-treatment in reference centers

In patients with rare diseases such as STS and GIST treatment in reference centers with multiprofessional expertise is mandatory to guarantee optimal management. Furthermore close multinational interconnection of clinicians and researchers is essential to offer the patients suitable clinical trials. In the light of the current development of a European reference network in rare cancers an interesting poster by Jean-Yves Blay was presented [17] (abstract 11013) reporting on the 5-year results of the French NetSARC network consisting of 26 reference multidisciplinary cancer centers aiming to improve the quality of care for sarcoma patients. The data consisted of 13,454 newly diagnosed patients with sarcomas and GIST representing an estimated 78 % of sarcoma case in France. LMS (12 %), GIST (8.2 %), dLPS (7.3 %), and UPS (11 %) were the most frequent histotypes. A higher number of patients managed in Netsarc centers had proper imaging of the primary tumor prior to surgery (86 % vs. 59 %, $p < 0.0001$), and had biopsy prior the first resection (80 % vs. 36 %, $p < 0.0001$). Patients whose primary surgery was performed in NetSARC centers had R0, R1, R2, and R (unknown or nonevaluable) surgery in 49, 27, 7, 16 % vs. 24, 31, 21, 23 % in centers outside NetSARC ($p < 0.000001$). Furthermore, 865 (19 %) patients had secondary resection after primary surgery in non-NetSARC centers vs. 252 (6 %) in NetSARC centers ($p < 0.0001$). Overall, progression-free survival (PFS) was better in patients managed in NetSARC reference centers ($p = 0.0008$). These data show clearly that sarcoma patients managed in reference centers have a significantly higher rate of R0 surgery, fewer reoperations, and better PFS. Importantly, between 2010 and 2015, the proportion of patients reviewed in NetSARC reference centers prior to surgery increased from 41 to 48 %.

Conclusion

Although new and successful treatment strategies as the immune checkpoint inhibitors have begun to transform the care of many cancer patients, the field of sarcoma immunotherapy is still in its early days. Importantly, successful STS therapy is still based on the importance of personalizing therapy considering histologic subtype, performance status, pace of disease progression, and comorbidities. When moving forward in the field of sarcoma, there are many open questions that remain unanswered and need to be addressed:

- Continuation in exploring the activity of immunomodulatory agents alone or in combinatorial approaches as well as consciousness of the potential of immune-mediated adverse events.
- Prospective clinical trials to investigate and determine the role of immune-related response and progression criteria.
- Determination and identification of predictive biomarkers.

Importantly, due to the rarity of STS and GIST and as illustrated by the latest data, diagnosis, treatment, and follow-up care should be reserved for reference centers with multiprofessional expertise to guarantee

optimal management throughout the complete disease trajectory.

Conflict of interest S. Roider-Schur, R. Hamacher, and T. Brodowicz declare that they have no competing interests.

References

1. Group, E.S.E.S.N.W. Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii102–iii112.
2. Eriksson M. Histology-driven chemotherapy of soft-tissue sarcoma. Ann Oncol. 2010;21(Suppl 7):vii270–vii276.
3. Reichardt P. Soft tissue sarcomas, a look into the future: different treatments for different subtypes. Future Oncol. 2014;10(8 Suppl):s19–s27.
4. Group, E.S.E.S.N.W.. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii21–iii26.
5. van der Graaf WT, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879–86.
6. Weber JS, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–84.
7. D'Angelo SP. Manipulating the immune system with checkpoint inhibitors for patients with metastatic sarcoma. Am Soc Clin Oncol Educ Book. 2016;35:e558–e564.
8. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691–7.
9. Penel N. Regorafenib (RE) in liposarcomas (LIPO), leiomyosarcomas (LMS), synovial sarcomas (SYN), and other types of soft-tissue sarcomas (OTS): Results of an international, double-blind, randomized, placebo (PL) controlled phase II trial. J Clin Oncol. 2016;34:(suppl; abstract 11003).
10. Schmoll HJ. Pazopanib vs pazopanib + gemcitabine in refractory soft tissue sarcoma: A randomized phase II trial of the AIO. J Clin Oncol. 2016;34:(suppl; abstr 11003).
11. Tawbi HA-H. Safety and efficacy of PD-1 blockade using pembrolizumab in patients with advanced soft tissue (STS) and bone sarcomas (BS): Results of SARC028–A multicenter phase II study. J Clin Oncol. 2016;34:(suppl; abstr 1106).
12. Lin Z, et al. PD-1 antibody monotherapy for malignant melanoma: A systematic review and meta-analysis. PLOS ONE. 2016;11(8):e0160485.
13. George S. Phase 2 study of nivolumab in metastatic leiomyosarcoma of the uterus. J Clin Oncol. 2016;34:(suppl; abstr 11007).
14. Von Mehren M. Dose escalating study of crenolanib besylate in advanced GIST patients with PDGFRA D842V activating mutations. J Clin Oncol. 2016;34:(suppl; abstr 11007).
15. DeMatteo RP, Targeting IDO. A novel immune checkpoint in GIST. oral presentation. 2016.
16. Balachandran VP, et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. Nat Med. 2011;17(9):1094–100.
17. Blay J-Y. Improved sarcoma management in a national network of reference centers: Analysis of the NetSarc network on 13,454 patients treated between 2010 and 2014. J Clin Oncol. 2016;34:(suppl; abstr 11013).

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