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SHORT COMMUNICATION

A pilot study of first-line olaratumab, doxorubicin and ifosfamide in patients with metastatic soft tissue sarcoma

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Abstract

Introduction Olaratumab (O) is a monoclonal antibody that specifically binds PDGFRα. The addition of O to doxorubicin (D) has been approved by the regulatory authorities for metastatic soft tissue sarcoma (MSTS). Since the combination of D + ifosfamide (I) is commonly used in MSTS and is associated with a higher response rate than D alone, it seems reasonable to combine O with the combination of D + I (ODI). We report our preliminary experience with O + D+I in MSTS.

Methods Between 01/01/2015 and 30/05/2018, 15 patients (pts) with MSTS were treated with ODI as first-line therapy. The treatment protocol consisted of IV D 50 mg/m^2 and I 5000 mg/m^2, day 1 (3 pts), or D 37.5 mg/m^2 and I 3000 mg/m^2 days 1–2 (12 pts). O (15 mg/kg) was given IV on days 1, 8, and cycles were repeated every 21 days.

Results With a median follow up of 16 months, 63 cycles of ODI were given. Objective response was achieved in 4 pts (27%) (CR in 3, PR in 1); 5 pts (33%) remained with stable disease for ≥ 5 mo. Median overall survival was 22 months. Major hematological toxicities (grade 3–4) included: neutropenia—7 pts (47%), and neutropenic fever—3 pts (20%). Non-hematological toxicities included grade 3 diarrheas in 2 pts (13%) after the second cycle. There was no treatment-related mortality.

Conclusion According to our preliminary experience, adding olaratumab to doxorubicin and ifosfamide is active and its safety profile is comparable to that of doxorubicin and ifosfamide alone in MSTS.

Keywords Olaratumab · Doxorubicin · Ifosfamide · Soft tissue sarcoma · Safety

Introduction

Soft tissue sarcomas (STS) are malignant tumors that arise in any of the mesodermal tissues of the extremities, trunk and retroperitoneum, or head and neck. The histological subtype can be helpful in treatment decision-making for some sarcoma subtypes. Nevertheless, anthracyclines (e.g. doxorubicin) remain the standard of care for first-line therapy in high-grade STS, regardless of subtype, presentation and patient characteristics [1].

Platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR) signaling play a significant part in mesenchymal biology, including mesenchymal stem cell differentiation, growth, and angiogenesis [2, 3]. The PDGF and PDGFR pathway is also involved in cancer through aberrant cellular signaling and has been implicated in modulating the tumor or stromal microenvironment and facilitating metastases in several malignancies [3, 4]. Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFRα, blocking PDGF-AA, PDGF-BB, and PDGF-CC binding and receptor activation [5].

In the phase II portion of an open-label phase Ib/II trial, the combination of doxorubicin and olaramatumab was compared to doxorubicin alone as first-line therapy in metastatic STS. Median overall survival (OS) was much longer with olaratumab plus doxorubicin compared to doxorubicin alone. In this study, adverse events that were more frequent in the combination arm included neutropenia, mucositis, nausea, vomiting and diarrhea. Febrile neutropenia of grade 3 or higher was similar in both the groups, 13–14% [6]. Importantly, the improvement in OS was achieved without a significant increase in serious (grade3–4) toxicity.

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Ifosfamide also has single-agent activity in STS [7] and, although not synergistic with anthracyclines, the two are often combined on the basis of improved response rates (RRs), progression-free survival (PFS) and palliation. In the first-line setting, the combination of doxorubicin and ifosfamide (AI) achieved a response rate of 12–34%, depending on subtypes, and disease control rates as high as 45–77% [8, 9].

Taking into consideration almost the same safety profile when combining olaratumab with doxorubicin, we decided that olaratumab in combination with doxorubicin and ifosfamide might also be safe enough, with higher response rates and probably a higher number of patients achieving long survival benefit.

Here we present a retrospective analysis of patients with metastatic STS, treated from 1/1/2015 to 30/5/2018, who received a combination of adriamycin, ifosfamide and olaratumab as first-line therapy.

Methods

The study included patients with advanced STS under treatment in the Division of Oncology at Rambam Health Care Campus (RHCC) in Haifa, Israel. In January 2015, olaratumab was approved in Israel for STS in combination with doxorubicin. The Sarcoma Unit in the Oncology Center, with the permission of the hospital ethics committee, decided that the combination of olaratumab–doxorubicin–ifosfamide (ODI) would be allowed in specific cases of STS. The study was approved by the hospital's institutional ethics committee (0208-18-RMB).

The ODI combination was given to patients 18 years or older with a diagnosis of advanced unresectable or metastatic STS, who were planned to be treated with combination of doxorubicin–ifosfamide to achieve a higher response rate or disease symptoms improvement. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a life expectancy of at least 3 months, measurable disease according to RECIST version 1.1, and adequate end-organ and hematopoietic functions.

Treatment protocols

Two schedules of chemotherapy were used (Table 1), with doxorubicin doses ranging from 50 to 75 m/m^2 per treatment. Ifosfamide was given in doses of 5000–6000 mg/m^2, respectively. Chemotherapy was given on day 1 or 1 and 2 every cycle (21 days each), up to a maximum of 8 cycles. The patients received olaratumab (15 mg/kg) intravenously on day 1 and day 8, with standard premedication. Primary prophylaxis with GCSF was routinely given after each cycle.

Patients

From 1/1/2015 to 30/5/2018, 15 patients with metastatic or unresectable STS were treated in RHCC with one of the study protocols. Patient characteristics are presented in Table 3. The median age was 55 years and 8 patients were female. Nine of the patients were in performance status (PS) 0. One-third of the patients were treated for unresectable tumors. Most of the patients were treated with the ODI-2 protocol, containing higher doses of doxorubicin and ifosfamide. The different subtypes of STS are presented in Table 2; the main histology subtypes were leiomyosarcoma (4 pts) and liposarcoma (3 pts).

Statistical analysis

All data were entered onto a Microsoft Excel spread sheet and analyzed using Fisher's Exact Tests, due to the small number of patients. OS and PFS were calculated by using Kaplan–Meier curves.

Table 1 Olaratumab, doxorubicin and ifosfamide treatment protocols and side effects

Olaratumab + Doxorubicin + Ifosfamide (low dose) (ODI 1)		Olaratumab + Doxorubicin + Ifosfamide (high dose) (ODI 2)	
Drug	Dose/day	Drug	Dose/day
Olaratumab	15 mg/Kg IV, days 1, 8	Olaratumab	15 mg/Kg IV, days 1, 8
Doxorubicin	50 mg/M^2 IV, day 1	Doxorubicin	37.5 mg/M^2 IV, days 1, 2
Ifosfamide	5000 mg/M^2 IV, day 1	Ifosfamide	3000 mg/M^2 IV, days 1, 2
Mesna (bolus)	600 mg/M^2 IV, day 1		
Mesna (continuous)	2500 mg/M^2 IV, day 1	Mesna (continuous)	3000 mg/M^2 IV, days 1, 2
Mesna (continuous)	1250 mg/M^2 IV, day 2	Mesna (continuous)	3000 mg/M^2 IV, day 3

Table 2 Treatment related side-effects

Type	Grade 1–2: *n* (%)	Grade 3–4: *n* (%)
Neutropenia	3 (20)	7 (46)
Febrile neutropenia		3 (20)
Anemia	6 (40)	4 (27)
Thrombocytopenia	3 (20)	2 (13)
Alopecia	15 (100)	
Diarrhea	1 (7)	2 (13)
LVEF decrease	0	0
Mucositis	1 (7)	0
Fatigue	8 (53)	
Nausea and vomiting	4 (27)	0
Other (Fanconi's syndrome)		1 (7)

Table 3 Patients and disease characteristics

Patients characteristics	Patient numbers
Number of patients	15
Female/male	8/7
Median age (range)	55 (19–77 years)
ECOG Performance status at treatment initiation: 0/1/2	9/5/1
Stage at diagnosis: III (unresectable)/IV	4/11
Stage IV—metastatic sites	11
Lungs	6
Liver (one patient with lung and liver mets)	3
Other—(peritoneum, muscle)	3
Treatment protocol: (ODI1/ODI2)	3/12
Histology	
Liposarcoma (mixoid cell type and dedifferentiated)	3
Leiomyosarcoma	4
Malignant fibrous histiocytoma	2
Synovial sarcoma	2
Myxofibrosarcoma	1
High grade epithelioid sarcoma	1
Undifferentiated uterine sarcoma	1
Malignant giant cell tenosynovial tumor	1

Results

Fifteen patients met the clinical criteria for treatment with one of the two combinations of doxorubicin and ifosfamide together with olaratumab as first line. First response evaluation was made after the 3rd cycle of treatment; those who progressed were immediately moved to second line or best supportive care, according to their general condition. Patients with stable disease or response continued chemotherapy until disease progression, severe side effects, or completion of 6–8 cycles (depending on the cumulative dose of doxorubicin according to the protocol). Patients whose disease did not progress on chemotherapy received olaratumab maintenance on day 1 and day 8 every 21 days, until progression.

Most of the patients (12) started therapy with full dose. However, full dose was given in all cycles to only 4 (27%). The dose reductions were of 10–15% from the initial dose. Overall, 63 cycles of ODI combinations were given (ODI1–10 cycles, ODI2–53 cycles). The median number of cycles per patient was four, in both treatment protocol types (range 2–8). Three patients in the group of ODI2 protocol started therapy with reduced doses (90%, 85%, 80%). Eight patients had dose reduction at the second cycle in 10–15%, most due to grade 3–4 neutropenia, regardless of primary prophylaxis with GCSF; other reasons were grade 3 diarrhea and fatigue grade 2. The number of cycles given prior to olaramatumab maintenance ranged between 2 and 8 (median 4) cycles.

With a median follow-up of 16 months (ranging 2–25), the objective response rate was 27% (4 pts); 3 pts had complete response and one had partial response. Five patients (33%) remained with stable disease during the treatment, leading to 60% clinical benefit.

Median PFS was 3 months, ranging from 2 to 19 months. Four patients (27%) reached 6 months without progression. Median overall survival was 22 months (range 2–25 months). At the time of analysis, 7 of 15 patients were still alive. Two underwent surgery for residual disease and stopped the treatment, and five other patients received second line, histology driven therapy.

Safety

The treatment was well tolerated. Nevertheless, 10 of 15 patients developed grade 3–4 adverse events, mostly hematological toxicity, neutropenia (46%) and febrile neutropenia (20%). In spite of the prophylactic use of GCSF, dose reduction was required in most of the patients. Four patients (27%) required red blood cell transfusion due to chemotherapy-related anemia, and 2 (13%) developed grade 3 thrombocytopenia that did not require platelets transfusion (Table 2).

The incidence of nausea and vomiting was generally low (27% Grade 1–2), due to the prophylactic use of highly potent agents, including palonosetron in combination with netupitant or aprepitant, according to the department protocol of prophylactics of chemotherapy-induced nausea and vomiting. Other gastrointestinal toxicity included mucositis (one pt) and diarrhea (20%, with 2 pts Gr 3 (13%)). One patient developed Fanconi's syndrome after the 2nd cycle of ODI2, manifested as hypophosphatemia, proteinuria, and glucosuria, probably secondary to ifosfamide. Alopecia was universal. No infusion-related reactions were reported.

Importantly, there was no treatment-related deaths during the study period.

Discussion

To the best of our knowledge, this study is the first safety report of treatment with ODI combination in naïve patients with metastatic STS. According to the results of a phase II trial, the combination of olaratumab and doxorubicin significantly improved overall survival [6] and was approved by the regulatory authorities for metastatic STS. Unfortunately, a phase III trial did not succeed to validate these results [10].

The combination of D + I led to significant 2.8 months improvement in median PFS, and a greater proportion of patients responded to the combination therapy than to doxorubicin alone [8, 11]. We assumed that a combination of all three drugs may lead to PFS and OS improvement. Based on the phase II study of olaratumab and doxorubicin, our hypothesis was that the toxicity of ODI combinations would not differ significantly from the same combinations without olaratumab and may achieve a better response in specific cases like high volume disease, symptomatic patient, or when rapid response is needed. This argument led to the permission of our local ethical committee to allow the use of this combination. The results of 3 out of 15 patients achieving CR and 60% of the patients with clinical benefit may justify this approach. However, a larger number of patients is needed to establish these combinations of olaratumab, doxorubicin and ifosfamide as a preferred treatment combination.

There are two ongoing phase 3 trials with olaratumab in advanced STS patients. The first is the ANNOUNCE trial that enrolled an estimated 460 patients with inclusion and exclusion criteria similar to those of the phase 1b/2 trial in order to assess a primary outcome of OS for doxorubicin plus olaratumab compared with doxorubicin plus placebo (NCT02451943) [10]. Unfortunately, an early report of the study results concludes that the primary endpoint of overall survival (OS) benefit with the combination of olaratumab plus doxorubicin was not achieved. In addition, the combination did not confirm clinical benefit compared to standard doxorubicin [10]. The second trial is the ANNOUNCE-2, an open-label phase 1b and randomized, double-blind phase 2 study evaluating gemcitabine and docetaxel with or without olaratumab for the treatment of advanced STS. The primary endpoint for the phase 1b was the identification of an olaratumab dose for phase 2, and the phase 2 primary endpoint is OS. This study is ongoing (NCT02659020) and study results are pending in the end of 2019 [12].

Olaratumab has been withdrawn by the sponsor in several jurisdictions based on results from recent Phase III trials. However, the results reported here encourage efforts to understand the biological and clinical bases for olaratumab action in responding patients.

In our study, the median PFS of 3 months, significantly lower than in previously reported combination trials [8, 11], was disappointing. This may be explained by the fact that the study population included a high proportion of patients with high burden disease, and large, unresectable tumors (median tumor diameter 9.5 cm, ranging 4–34 cm). The response rate reported in our study reached 27%, and another 30% of the patients remained with stable disease. When looking at other trials with a similar treatment strategy (doxorubicin–ifosfamide, without olaratumab) [8, 11], the response rates were similar, but the rate of neutropenic fever was obviously lower in the current study (20% in our trial vs 40–46% in others). This may be explained by the prophylactic use of GCSF in all our patients. The most frequent grade 3 toxicity was hematologic toxicity, including 7 patients with grade 3 neutropenia, three with febrile neutropenia; 4 patients with anemia and 2 with grade 3 thrombocytopenia. Among less common grade 3 side effects were two cases of diarrhea and one case of Fanconi's syndrome. There was no decrease in ejection fraction in all study population and also no infusion-related reactions.

Conclusion

According to this pilot study, adding olaratumab to doxorubicin and ifosfamide in patients with advanced STS is relatively safe. The combination of these 3 drugs is active in those patients and its safety profile comparable to that of doxorubicin and ifosfamide alone.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Singer S, Demetri GD, Baldini EH, Fletcher CD (2000) Management of soft-tissue sarcomas: an overview and update. Lancet Oncol 1:75–85
2. Ng F, Boucher S, Koh S, Sastry KS, Chase L, Lakshmipathy U, Choong C, Yang Z, Vemuri MC, Rao MS, Tanavde V (2008) PDGF, TGF-beta, and FGF signaling is important for differentiation and growth of mesenchymal stem cells (MSCs): transcriptional profiling can identify markers and signaling pathways important in differentiation of MSCs into adipogenic, chondrogenic, and osteogenic lineages. Blood 112:295–307. https://doi.org/10.1182/blood-2007-07-103697
3. Chen CY, Liu SH, Chen CY, Chen PC, Chen CP (2015) Human placenta-derived multipotent mesenchymal stromal cells involved

in placental angiogenesis via the PDGF-BB and STAT3 pathways. Biol Reprod 93:103. https://doi.org/10.1095/biolreprod.115.131250
4. Ostman A, Heldin CH (2001) Involvement of platelet-derived growth factor in disease: development of specific antagonists. Adv Cancer Res 80:1–38
5. Loizos N, Xu Y, Huber J et al (2005) Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumour xenografts: implications as a potential therapeutic target. Mol Cancer Ther 4:369–379
6. Tap WD, Jones RL, Van Tine BA, Chmielowski B (2016) Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 30(388):488–497. https://doi.org/10.1016/S0140-6736(16)30587-6
7. Leyvraz S, Zweifel M, Jundt G, Swiss Group for Clinical Cancer Research et al (2006) Long-term results of a multicenter SAKK trial on high-dose ifosfamide and doxorubicin in advanced or metastatic gynecologic sarcomas. Ann Oncol 17:646–651
8. Judson I, Verweij J, Gelderblom H, Hartmann JT (2014) Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 15:415–423. https://doi.org/10.1016/S1470-2045(14)70063-4
9. Ryan CW, Merimsky O, Agulnik M et al (2016) PICASSO III: a phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. J Clin Oncol 34:3898–3905. https://doi.org/10.1200/JCO.2016.67.6684
10. Tap WD, et al (2019) ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). Abstract LBA3. ASCO Meeting, Chicago USA
11. Le Cesne A, Judson I, Crowther D et al (2000) Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol 18:2676–2684
12. http://fdaaa.trialstracker.net/trial/NCT02659020/