Efficacy of combination-chemotherapy with pirarubicin, ifosfamide, and etoposide for soft tissue sarcoma: A single-institution retrospective analysis

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Abstract

Background: The standard chemotherapy regimens for soft tissue sarcoma are doxorubicin-based. This phase 2 study aimed to assess the efficacy and safety of pirarubicin, ifosfamide, and etoposide combination therapy for patients with this disease.

Methods: Between 2008 and 2017, 25 patients with soft tissue sarcoma were treated with pirarubicin (30 mg/m^2, 2 days), ifosfamide (2 g/m^2, 5 days), and etoposide (100 mg/m^2, 3 days) every 3 weeks. The primary endpoint was overall response, and the secondary endpoint was adverse events of this regimen.

Results: Response to this regimen according to RECIST criteria was 36% PR (n = 9), 36% SD (n = 9) and 28% PD (n = 7). During the treatment phase, frequent grade 3 or worse adverse events were haematological toxicities including white blood cell decreases (96%), febrile neutropenia (68%), anemia (68%), and platelet count decreases (48%). No long-term adverse events were reported during the study period.

Conclusion: This regimen was comparable to previously published doxorubicin-based combination chemotherapy in terms of response rate. Although there were no long lasting adverse events, based on the results, severe haematological toxicity should be considered.

Background

Soft tissue sarcomas are malignant tumours that can originate in soft tissues throughout the body; they comprise approximately 0.7% of all adult malignant tumours (1). The definitive therapy for localized soft tissue sarcomas is surgical excision, whereas chemotherapy is administered to patients with metastases or unresectable lesions to prolong survival or delay cancer progression. The standard first-line regimen for patients with advanced soft tissue sarcomas remains doxorubicin (Adriamycin [ADR]) monotherapy, although the effectiveness of this treatment is not high (2,3).

Pirarubicin (4'-O-tetrahydropyranyl doxorubicin [THP]) is an anthracycline antineoplastic antibiotic discovered by Umezawa et al that can act as a substitute for ADR (4). THP inhibits DNA synthesis by interacting with topoisomerase II, thereby exhibiting an antitumor effect. In past studies, the uptake velocity of THP was found to be approximately 170 times faster than that of ADR, while its cardiotoxicity was lower (5,6). Furthermore, the THP dose limit is expected to be almost twice that of ADR (950 mg/m^2 vs 500 mg/m^2). However, the efficacy and safety of THP for soft tissue sarcomas has not been fully validated in clinical settings.

In this study, we retrospectively investigated the efficacy and safety of the novel combination of THP, IFO, and VP-16 against soft tissue sarcoma. The primary endpoint of this study was the overall response to the chemotherapy, and the secondary endpoint was the safety of this chemotherapy regimen in terms of adverse events.

Methods

Patients

The combination therapy with THP, IFO and VP-16 regimen was considered to be first line for patients fulfilling the following criteria; presence of metastatic tumors and neoadjuvant chemotherapy for locally aggressive primary tumor with/ without oligometastases. The following criteria were included: diagnosed with grade 2 or 3 soft tissue sarcoma (according to the Fédération Nationale des Centres de Lutte Contre le Cancer) (7), non-round cell type, Eastern Cooperative Oncology Group performance status scores of 0 – 2, under 70 years of age, and received no prior chemotherapy for soft tissue sarcoma. Before induction into the study, as well as at the beginning of every chemotherapy cycle, patients were evaluated for kidney (creatinine clearance > 60 mL/min), heart (ejection fraction > 60%), and liver (within 2.5 fold the upper limit of normal for alanine aminotransferase, aspartate aminotransferase, and total bilirubin) function. One hundred eighty eight patients diagnosed with soft tissue sarcoma in Nagoya City University hospital between 2008 and 2017 were initially included in this study. We excluded 62 patients with low-grade sarcomas, 7 with small round cell tumour, 91 who underwent definitive surgical resection without chemotherapy, and 2 who were treated with other chemotherapy regimens (Figure 1). Finally, 25 patients who met the criteria were included. The study was performed according to the principles laid out in the Declaration of Helsinki of 1964. The ethical committee of the Nagoya City University Hospital approved the combination therapy as a phase II clinical study and this retrospective analysis. Written informed consent for the administration of this combination therapy was obtained from all patients and their families.

Procedures

During 2–3 weeks of hospitalization, patients were treated with THP (30 mg/m^2, days 1 and 2), IFO (2 g/m^2, days 1–5), and VP-16 (100 mg/m^2, days 1–3) via intravenous infusion. The doses of the chemotherapeutic agents were reduced by 20% if adverse events occurred or were expected to occur. Treatment was repeated every 3 weeks to allow for full recovery from haematological toxicities. The treatment was terminated upon tumour progression (as verified via imaging), attaining the dose limit for cardiotoxicity (the maximal total dose of THP was limited to 950 mg/m^2 with safety margins), occurrence of severe adverse events (except for haematological toxicities), or patient withdrawal.

Radiological assessment of the target lesions was performed using computed tomography or magnetic resonance imaging before and after every treatment cycle, with the outcome classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on the Response Evaluation Criteria In Solid Tumours version 1.1 [8]. Radiographical evaluations were performed by independent radiologists.

The adverse events of treatment were graded according to the Common Terminology Criteria for Adverse Events, version 5.0, based on a review of laboratory test results and medical charts.

Results

Twenty-five patients (male = 17, female = 8) with a median age of 51 years who were treated with THP, IFO, and VP-16 combination therapy were included in the study. Seven patients underwent this regimen as neoadjuvant chemotherapy, and 18 patients were treated to control surgically unresectable sarcoma or metastatic tumors. Histological subtypes included synovial sarcoma (n = 7, 28%), undifferentiated pleomorphic sarcoma (n = 6, 24%), myxofibrosarcoma (n = 3, 12%), epithelioid sarcoma (n = 2, 8%), myxoid liposarcoma (n = 2, 8%), alveolar soft part sarcoma (n = 2, 8%), and others (n = 3, 12%). Their characteristics are shown in Table I with additional details supplied in the Supplementary Table. As for the best responses to chemotherapy, 9 patients were evaluated as PR (the overall response rate = 36%), while 9 patients were classified as having SD and 7 had PD.

Serious adverse events of grade 3 or higher were white blood cell decreases (96%), febrile neutropenia (68%), anemia (68%), platelet count decreases (48%), Alanine aminotransferase increases (20%), and Aspartate aminotransferase increases (12%). These adverse events were appropriately managed with blood transfusion, G-CSF administration, or the induction of short-term antibiotics. None of these treatment-related serious adverse events were fatal. The non-hematological toxicities were relatively tolerable, while 2 patients discontinued chemotherapy because of delirium or urticaria. During the study, there were no cases of cardiac or renal toxicity reported (Table II).

Case presentation

A 67-year-old man with a tumor in the right anterior chest wall was referred to our department. The patient was diagnosed with high grade myxofibrosarcoma by needle biopsy. Although there was no metastatic lesion, the tumor was located in his pectoralis minor muscle and adjacent to his ribs, brachial plexus, subclavian artery and vein (Figure 2a, 2b).

The patient received THP, IFO and VP-16 as neoadjuvant chemotherapy. Six cycles were performed, and adverse events of grade 3 or higher were white blood cell decrease, febrile neutropenia, anemia, and platelet count decrease, lower than grade 2 toxicities were alopecia, fatigue and nausea. After chemotherapy, the tumor showed remarkable shrinkage (Figure 2c, 2d), and tumor resection was performed. Although wide resection including a part of the pectoralis major muscle and pectoralis minor muscle was performed, rib, nerves and blood vessels were spared. Histological evaluation, showed hyaline or sclerotic change in most tumor cells (Figure 2f, 2g) and the surgical margin was negative. The patient received a further three courses of adjuvant chemotherapy with this regimen after surgery. No evidence of disease and no signs of recurrence were seen at outpatient follow-up 2 years after the definitive surgery.

Discussion

In this study, we showed that the combination therapy of THP + IFO + VP-16 was effective for patients with soft tissue sarcomas, with an overall response rate of 36%. To date, ADR monotherapy is considered

the standard first-line treatment for advanced soft tissue sarcoma (9). This is based on a randomized controlled phase III trial of ADR monotherapy versus ADR + IFO combination therapy for the first-line treatment of patients with this disease (10). Although the response rate and progression-free survival (PFS) were significantly improved in the combination group, adverse events were more frequent and there was no significant difference in overall survival (OS) between the 2 groups (10). Therefore, ADR monotherapy has been recommended for delaying tumour progression or alleviating tumour-related symptoms with acceptable adverse events. Conversely, ADR + IFO combination therapy is recommended when tumour shrinkage is expected to be beneficial, such as in patients experiencing severe symptoms caused by tumors compressing adjacent essential organs or in those intending to convert to resectable status for their primary or metastatic lesions. The regimen in our study (THP + IFO + VP-16) was comparable to ADR + IFO combination therapy in its efficacy, although patients with grade 3 or higher hematological toxicities should be monitored (Table III).

A similar combination regimen comprising 4 cycles of VP-16 (125 mg/m^2) + IFO (1500 mg/m^2) + ADR (50 mg/m^2) (i.e., an “EIA regimen”) with the addition of G-CSF to treat any perioperative conditions was reported by Schmitt et al in 2010 (11). According to their data, the response to this regimen was CR, PR, SD, and PD in 6%, 24%, 62%, and 8% of their patients, respectively. However, grade 2 cardiac toxicity occurred in 4% of their patients. Originally, this EIA regimen was reported by Issels et al in a phase III trial that included regional hyperthermia (12). Although this study showed promising results in terms of combining hyperthermia with EIA, secondary leukaemias were also reported in 5 patients, and 3 patient deaths were attributed to the treatment. Therefore, the investigators concluded that the EIA regimen should be discontinued in further studies due to the risk of leukaemia owing to VP-16 administration. Despite no secondary leukaemia occurring among our own patients, the administration of VP-16 should be considered in a prudent manner.

This study had several limitations. First, it was performed at a single institution and had a small sample size, which may have biased the results. Because of the versatile histology of soft tissue sarcoma, the responses to chemotherapy can vary considerably among patients; hence, our results should be interpreted with caution. Nevertheless, we showed that our regimen was superior to ADR monotherapy in terms of response.

Conclusion

We retrospectively analysed the clinical effect of combination THP, IFO, and VP-16 in patients with soft tissue sarcomas. Although the response to this chemotherapy regimen was superior to ADR monotherapy, severe haematological toxicity should be considered.

Abbreviations

ADR: Adriamycin, AN: anemia, ASPS: alveolar soft part sarcoma, AWD: alive with disease, CR: complete response, DOD: died of disease, ES: epithelioid sarcoma, FN: febrile neutropenia, G-CSF: granulocyte-

colony stimulating factor, IFO: ifosfamide, LP: leukopenia, MFS: myxofibrosarcoma, MLS: myxoid liposarcoma, NED: no evidence of disease, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PR: partial response, PS: performance status, RECIST: Response Evaluation Criteria In Solid Tumours, SD: stable disease, SS: synovial sarcoma, THP: 4’-O-tetrahydropyranyl doxorubicin, TP: thrombocytopenia, UPS: undifferentiated pleomorphic sarcoma, VP-16: Etoposide

Declarations

Ethics approval and consent to participate

This study was approved by the ethical committee of Nagoya City University Hospital, and informed consent was obtained from all patients and their families.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusion of this article are included within the article. The underlying datasets are available from the author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SS and HA designed this study, reviewed the clinical records, analyzed the data and wrote the manuscript. SM participated in the study design, data interpretation, and discussion. All authors read and approved the final manuscript.

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Tables

Table I. Patients’ characteristics

Patient's characteristics		Patients treated with THP + IFO + VP-16 (N=25)
Age (mean, standard deviation)		48, 15
Sex	Male / Female	17 / 8
Histology	Synovial sarcoma	7
	Undifferentiated pleomorphic sarcoma	6
	Myxofibrosarcoma	3
	Epithelioid sarcoma	2
	Myxoid liposarcoma	2
	Alveolar soft part sarcoma	2
	Others	3
Original localization	Upper extremity	3
	Lower extremity	12
	Trunk	10
Performance status	0 / 1 / 2 / 3 / 4	13 / 6 / 6 / 0 / 0
Reason for chemotherapy	Neoadjuvant chemotherapy	7
	Unresectable or metastatic tumors	18

Others = leiomyosarcoma, intimal sarcoma, and malignant peripheral nerve sheath tumor

Table II. Adverse events according to the Common Terminology Criteria for Adverse Events, version 5.0.

Adverse event, n (%)	Grade 1-2	Grade 3-4
White blood cell decreased	1 (4)	24 (96)
Anemia	8 (32)	17 (68)
Febrile neutropenia	-	17 (68)
Platelet count decreased	13 (52)	12 (48)
Alanine aminotransferase increased	3 (12)	5 (20)
Aspartate aminotransferase increased	5 (20)	3 (12)
Alopecia	25 (100)	0 (0)
Nausea	17 (68)	0 (0)
Fatigue	11 (44)	0 (0)
Constipation	8 (32)	0 (0)
Diarrhea	8 (32)	0 (0)
Dyspepsia	7 (28)	0 (0)
Hiccups	6 (24)	0 (0)
Vomiting	5 (20)	0 (0)
Mucositis oral	4 (16)	0 (0)
Insomnia	3 (12)	0 (0)
Hematuria	2 (8)	0 (0)
Dysgeusia	2 (8)	0 (0)
Arthralgia	2 (8)	0 (0)
Urticaria	1 (4)	0 (0)
Delirium	1 (4)	0 (0)
Creatinine increased	0 (0)	0 (0)
Heart failure	0 (0)	0 (0)

Table III. The comparison of first-line treatments for patients with soft tissue sarcoma

Chemotherapy regimen	Overall response (CR + PR)	Adverse events (> Grade3)
Doxorubicin monotherapy (10)	14%	LP = 18%, FN = 13%, AN = 4%, TP = 0.4%
Doxorubicin + ifosfamide (10)	26%	LP = 43%, FN = 46%, AN = 35%, TP = 33%
Gemcitabine + docetaxel (13)	20%	LP = 7%, FN = 12%, AN = 6%, TP = 0%
Current protocol	36%	LP = 96%, FN = 68%, AN = 68%, TP = 48%

CR = complete response, PR = partial response, LP = leukopenia, FN = febrile neutropenia, AN = anemia, TP = thrombocytopenia

Figures

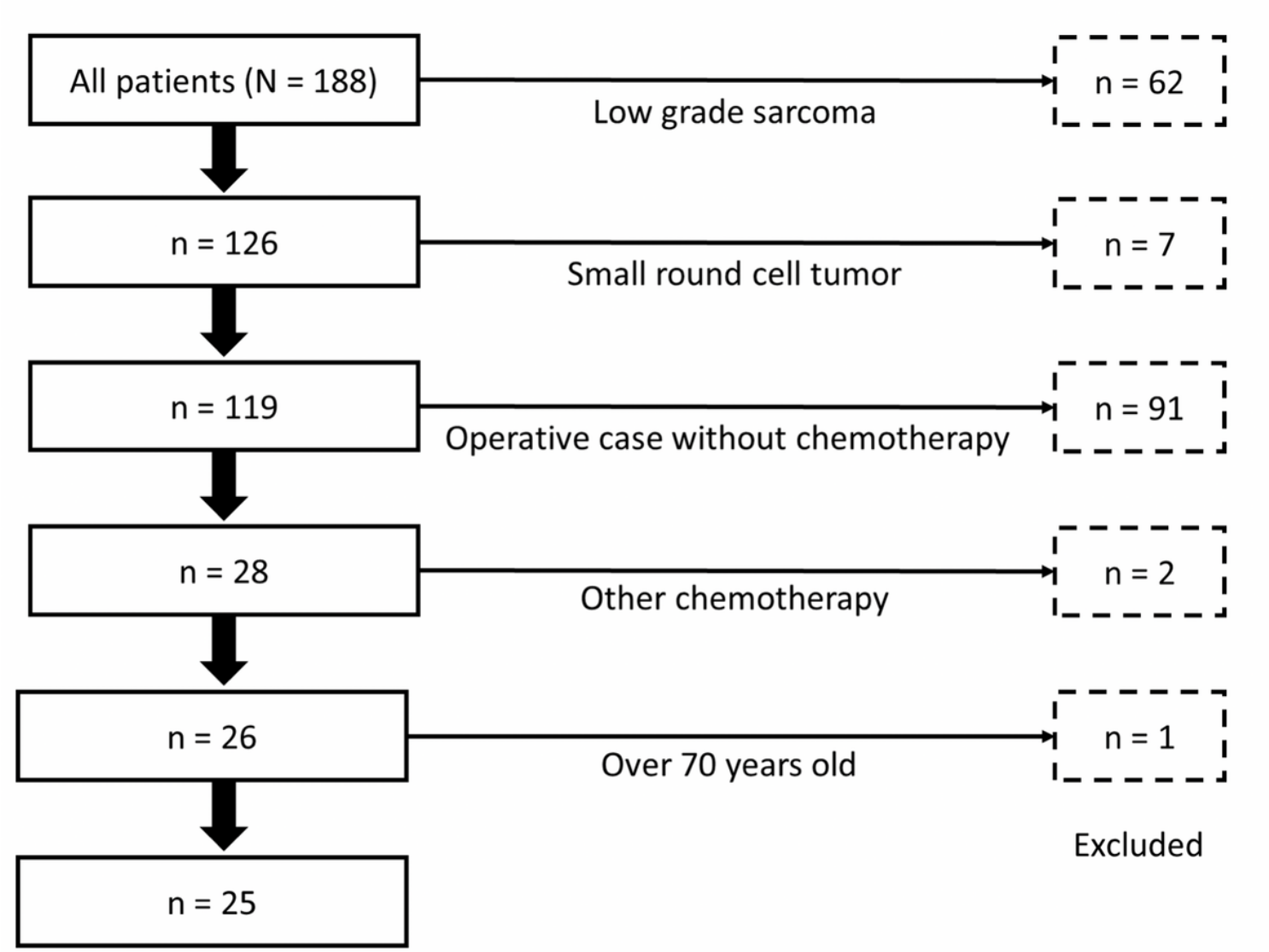

Figure 1

A CONSORT diagram of the patient selection process.

Figure 2

Representative case (Pt number 15). A patient (67-year-old male), complained of soft tissue mass at the right chest wall for 4 months. The diagnosis was confirmed by needle biopsy as high-grade myxofibrosarcoma. Neoadjuvant chemotherapy was administered with the aim of improving local control and preserving neurovascular bundles. (a, b) MRI (T2 weighted-image) and 3D-CT images of the tumor before chemotherapy. The tumor (9cm × 7cm × 4cm) was located in the pectoralis minor muscle, adjacent to the ribs, brachial plexus, subclavian artery and vein. (c, d) MRI (T2 weighted-image) and 3D-CT images after six cycles of chemotherapy. The tumor showed remarkable shrinkage (5cm × 2cm × 3cm). (e) Histological image of the biopsy specimen showing presence of proliferated spindle cells and myxoid modification. The diagnosis was high-grade myxofibrosarcoma. (f) Histological image of the

resected specimen showing hyaline or sclerotic changes in most tumor cells. The response for neoadjuvant chemotherapy was evaluated as over 90% based on the necrotic or degenerative area. (g) Image of the resected specimen. The boundary between the viable and degenerative areas is shown in (f).