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CLINICAL TRIAL REPORT

Phase I Trial of Pegylated Liposomal Doxorubicin Combined with Ifosfamide for Advanced Soft Tissue Sarcoma

Ting Ye[1,2], Li Fan[1], Rubo Cao[1], Ling Peng[1], Jing Chen[1,3]

[1]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, People's Republic of China; [2]Hubei Key Laboratory of Precision Radiation Oncology, Wuhan, 430022, People's Republic of China; [3]Institute of Radiation Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, People's Republic of China

Correspondence: Jing Chen, Email chenjingwh@hust.edu.cn

Introduction: This study aimed to determine the maximum tolerated dose (MTD) of pegylated liposomal doxorubicin (PLD) combined with both ifosfamide (IFO) and supported by human granulocyte colony-stimulating factor (rhG-CSF) for treating advanced soft tissue sarcoma (STS).

Methods: Twenty-three patients were enrolled in this trial with 3+3 dose-escalation from January 2020 to September 2022. PLD was initiated at 30 mg/m^2 and incrementally escalated by 5 mg/m^2 per step. MTD was the primary endpoint, and the safety profile served as the secondary endpoint.

Results: Two patients treated with PLD (55 mg/m^2) experienced dose-limiting toxicities. Ultimately, the MTD of PLD was established as 50 mg/m^2 (single cycle) in combination of IFO (3 g/m^2/day for days 1–3) and supported by rhG-CSF. Across all dose levels, common grade 3/4 adverse events included leukopenia (86.96%), neutropenia (82.61%), and lymphopenia (56.52%). Twelve of the 23 patients voluntarily chose to continue treatment with this regimen. The overall response rate was 33.33% (95% confidence interval: 9.92–65.11), and the disease control rate was 83.33% (95% confidence interval: 51.59–97.91).

Conclusion: This study successfully determined the MTD of PLD in combination with IFO and rhG-CSF for advanced STS, offering a potentially valuable treatment option with a tolerable safety profile.

Keywords: soft tissue sarcomas, pegylated liposomal doxorubicin, ifosfamide, dose-escalation, safety

Introduction

Soft tissue sarcoma (STS) is a malignant tumor that originates in the body's soft tissues, including the muscles, nerves, fibrous tissues, blood vessels, and deep skin tissues, and it represents approximately 0.69% of all adult malignancies.[1] The incidence of STS varies by region, with rates of 2.91 per 100,000 in China,[2] 3.24 per 100,000 in the United States,[3] and up to 9 per 100,000 in Europe.[4] Surgical removal remains the fundamental treatment for localized, resectable STS, though more than half of these patients eventually develop local recurrences or distant metastases.[5] Since the 1980s, doxorubicin-based chemotherapy has been the standard care for patients with unresectable or metastatic STS. In recent years, targeted therapies like antiangiogenic tyrosine kinase inhibitors and immunotherapies such as immune checkpoint inhibitors have been tested in various tumors, including some advanced or metastatic STS histological types.[6,7] Despite these efforts, only a limited number of patients have shown significant treatment responses, and the overall survival (OS) rates have not substantially improved.[8,9] Chemotherapy remains the predominant treatment for most patients with advanced STS.

Doxorubicin remains the primary drug used for treating advanced STS, yet its efficacy alone falls short compared to combination therapies. The EORTC62012 study, a major Phase III randomized controlled trial, demonstrated that combining doxorubicin with ifosfamide (IFO) significantly enhanced the overall response rate (ORR, 26% vs 14%, $p<0.0006$) and progression-free survival (PFS, 7.4 months vs 4.6 months, $p=0.003$) for the first-line treatment of

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advanced STS compared to doxorubicin alone.[10] Despite these benefits, the combination did not improve OS, likely due to a higher incidence of discontinuation of treatment for toxic effects compared to doxorubicin alone (18% vs 3%).[10,11] Thus, reducing the toxicity of doxorubicin combined with IFO is crucial for enhancing the OS.

Pegylated liposomal doxorubicin (PLD) is a specialized form of doxorubicin that is encapsulated within liposomes, with a polyethylene glycol modification on its surface that hinders recognition and clearance by the mononuclear phagocytic system, thus extending its circulation time in the blood. The large size and lipid composition of PLD molecules prevent easy penetration through normal vascular walls, leading to minimal distribution in healthy tissues. Conversely, due to the enhanced permeability of blood vessels in solid tumors, PLD can more easily enter tumor blood vessels and accumulate within the tumor tissue. This targeted delivery allows PLD to have a significantly reduced toxicity compared to traditional doxorubicin, making it a preferred alternative for various tumor types.[12,13] In a randomized controlled trial, PLD demonstrated comparable efficacy to doxorubicin in treating STS but with a better toxicity profile.[14] Consequently, the National Comprehensive Cancer Network guidelines now recommend PLD as a first-line treatment option for advanced or metastatic STS.[15] To enhance treatment outcomes, the potential for combining PLD with other drugs such as IFO is being explored. For example, in a phase I trial,[16] a combination therapy with PLD (Caelyx) at doses of 30 mg/m² or 40 mg/m² and various doses of IFO was tested for the treatment of advanced or metastatic STS. The study concluded that the recommended dose should be Caelyx at 30 mg/m² over 1 h on day 1, combined with IFO at 3 g/m² over 4 h on days 1–3, administered every 3 weeks. Moreover, in this study, the incidence of grade 3–4 neutropenia was 3/6 under the recommended dose, but no dose-limiting toxicity (DLT) was achieved and no febrile neutropenia (FN) occurred. Research has consistently shown that higher doses of doxorubicin can boost the effectiveness of STS treatments.[17–19] Despite the valuable insights and guidelines established by the study nearly two decades ago, it identified the MTD without the use of recombinant human granulocyte colony-stimulating factor (rhG-CSF), which can alleviate myelosuppression caused by chemotherapy. With rhG-CSF support, there is potential to increase the PLD dose, possibly enhancing therapeutic outcomes.

This phase I study aimed to determine the MTD and to assess the safety of escalated doses of PLD in combination with a fixed dose of IFO, supported by rhG-CSF, in advanced STS patients. The findings are expected to inform optimal PLD dosing strategies for combined therapy in clinical practice. The initial PLD dose was set at 30 mg/m^2, paired with a consistent IFO dose (3 g/m^2/day, days 1–3).

Methods

Study Design and Subjects

This Phase I, single-center, dose-escalation study received approval from the Clinical Trial Ethics Committee of Huazhong University of Science and Technology, with ethics approval number [2019] (25)-2. It was registered with the Chinese Clinical Trial Registry under the identifier ChiCTR1900028270. Prior to participation, all subjects gave written informed consent. The study adhered to the principles of the Declaration of Helsinki[20] and Good Clinical Practice.

Eligible participants included patients with advanced STS independently diagnosed by two senior experts in tumor pathology based on postoperative pathological sections. The key criteria for inclusion were as follows: 1) An age between 18 and 70 years; 2) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and 3) normal bone marrow hematopoietic and heart functions. Patients with STS subtypes not amenable to treatment with PLD+IFO, such as those with a gastrointestinal stromal tumor, embryonal/acinar rhabdomyosarcoma, or Ewing's sarcoma, were excluded. Further details regarding the inclusion and exclusion criteria are available in the supplementary material 1.

Procedures

The patients enrolled in this study were administered a regimen consisting of PLD (Duomeisu®, CSPC Ouyi Pharmaceutical Co. Ltd.) and IFO at 3 g/m^2/day on days 1–3, as well as mesna at 600 mg/m^2 given concurrently with IFO, which was administered at 0 h, 4 h, and 8 h post-IFO infusion, separately for three days. The initial dose of PLD was 30 mg/m^2, incrementally increasing by 5 mg/m^2 up to a maximum of 70 mg/m^2 using a 3+3 step-up dosing regimen (refer to Figure 1).[21] rhG-CSF was administered at 48 h following the chemotherapy.

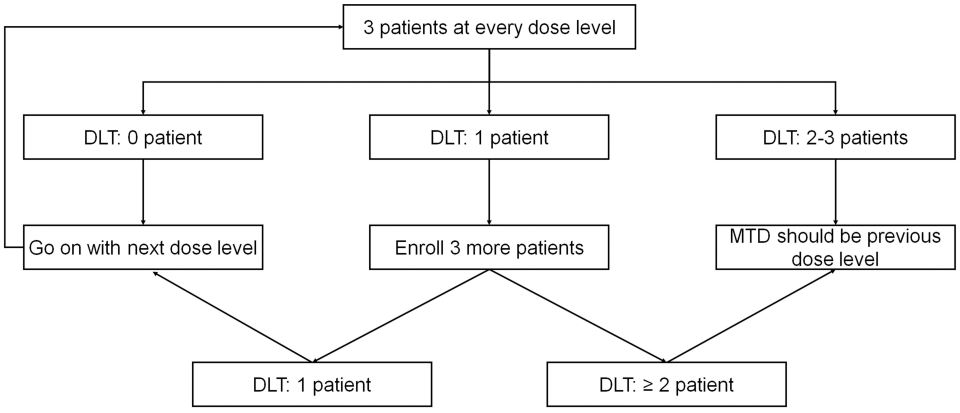

Figure 1 Study design.

Following the administration of chemotherapy, the DLTs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. This assessment continued until 28 days after the chemotherapy or before the commencement of any subsequent antitumor therapy. After the completion of chemotherapy administration, blood routine test should be conducted every other day. If the patient experiences grade 4 bone marrow suppression during this period, treatment should be provided according to clinical protocols, and blood routine test should be performed daily. Once the patient recovers from grade 4 bone marrow suppression, blood routine test should revert to every other day until the criteria for discontinuing testing are met. Liver and kidney function tests, as well as urine routine tests, should be rechecked on the first day after chemotherapy and then weekly thereafter; electrocardiograms and cardiac echography should be re-evaluated three weeks after chemotherapy. DLTs assessed included the following: (i) FN lasting three days or more; (ii) grade 4 neutropenia lasting five days or more; (iii) hemoglobin levels below 60 g/L; (iv) grade 4 thrombocytopenia lasting three days or more without platelet transfusions; (v) grade 4 thrombocytopenia post-platelet transfusion with a recurrence of grade 4 thrombocytopenia; (vi) platelet count below 10×10^9/L; (vii) grade 3 or 4 thrombocytopenia with a risk of hemorrhage; (viii) grade 3 or 4 nonhematologic toxicity excluding nausea, and vomiting; (ix) cardiotoxicity of grade 2 or higher; and (x) any toxicity causing a delay in chemotherapy of more than two weeks (as specified in the supplementary material 2).

Endpoints

The primary endpoint of this study was the MTD, defined as the highest dose below which no more than 33% of the patients experienced a DLT within the first 21 days of treatment. The secondary endpoint focused on the safety profile of the regimen, evaluated through the incidence of adverse events (AEs) as classified by the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

Statistical analysis was conducted using SAS software, version 8.1. The sample size at each dose level was determined based on observed toxicity levels rather than predefined statistical parameters. All analyses were carried out on the safety set, which included all participants who received at least one dose of the treatment and for whom safety data were available. Categorical data were presented as counts and percentages, while continuous data were summarized as medians with their respective ranges.

Results

Patient Characteristics

From January 2020 to September 2022, a total of 23 patients were enrolled in this study, comprising 12 males (52.17%) and 11 females (47.83%). The median age of the participants was 49 years, with ages ranging from 30 to 68 years. At the time of enrollment, the majority of patients, 16 (69.57%), had an ECOG PS score of 0, and 7 (30.43%) had an ECOG PS

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score of 1. The distribution of cancer stages among the participants was predominantly advanced, with 22 patients (95.65%) diagnosed with American Joint Committee on Cancer stage IV disease, and 1 patient (4.35%) with stage III disease at study entry. This study encompassed a variety of tumor subtypes, with fibrosarcoma being the most prevalent, affecting four patients. The detailed characteristics of the patient cohort are provided in Table 1.

Dose Escalation

During the dose-escalation phase, no DLTs were observed at PLD doses ranging from 30 to 50 mg/m^2. However, upon administration of PLD at 55 mg/m^2, two patients (patients 1 and 5) experienced DLTs. This prompted the inclusion of an additional three patients at the 50 mg/m^2 dose level (Table 2). These patients did not exhibit any

Table 1 Demographic and Clinical Characteristics of the Patients Included in This Study

Characteristic	No. of Patients	%
Sex		
Male	12	52.17
Female	11	47.83
Age, years (range)	49 (30–68)	
ECOG PS		
0	16	69.57
1	7	30.43
Stage		
III	1	4.35
IV	22	95.65
No. of involved organs		
0	1	4.35
1	16	69.57
≥1	6	26.09
Location of tumor		
Legs	8	34.78
Visceral	4	17.39
Arms	2	8.70
Back	2	8.70
Abdominal cavity	2	8.70
Hip	2	8.70
Neck or Jaw	2	8.70
Thorax	1	4.35
Histologic subtype		
Fibrosarcoma	4	17.39
Synovial sarcoma	3	13.04
Leiomyosarcoma	3	13.04
Malignant peripheral nerve sheath tumor	2	8.70
Undifferentiated sarcoma	2	8.70
Liposarcoma	1	4.35
Myxoid liposarcoma	1	4.35
Dedifferentiated liposarcoma	1	4.35
Epithelioid sarcoma	1	4.35
Unclassifiable soft tissue sarcoma with rhabdomyocyte differentiation	1	4.35
Pleomorphic rhabdomyosarcoma	1	4.35
Epithelioid hemangioendothelioma	1	4.35
Angiosarcoma	1	4.35
Malignant granular cell tumor	1	4.35

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2 Dose Escalation of PLD

Level	PLD Per Day	No. of Patients	No. of Patients Experiencing at Least a DLT	No. of DLTs
1	30 mg/m^2	3	0	0
2	35 mg/m^2	3	0	0
3	40 mg/m^2	3	0	0
4	45 mg/m^2	3	0	0
5	50 mg/m^2	6	0	0
6	55 mg/m^2	5	2	5

Abbreviations: DLT, dose-limiting toxicity; PLD, pegylated liposomal doxorubicin.

DLTs, establishing the MTD for PLD as 50 mg/m^2, when combined with IFO (3 g/m^2/day, days 1–3) and supported by rhG-CSF.

The specific DLTs for one patient were grade 4 neutropenia lasting longer than five days (specifically, six days). Both conditions improved to below grade 1 after 13 and 10 days, respectively. The second patient experienced grade 4 neutropenia lasting eight days, grade 4 thrombocytopenia that recurred post-platelet transfusion, and grade 3 alanine aminotransferase elevation. The neutropenia and elevated alanine aminotransferase levels improved to below grade 1 after 10 and 9 days, respectively, and the thrombocytopenia returned to grade 2 within three days following a recurrence.

Safety

The AEs observed during this study are detailed in Table 3. Hematological toxicities were the most prevalent side effects, with neutropenia, leukopenia, and lymphopenia each affecting 21 out of 23 participants (91.30%). Nonhematological

Table 3 Adverse Events That Occurred in This Study

Adverse event	All (N=23)		Level 1&2 (N=6)		Level 3&4 (N=6)		Level 5 (N=6)		Level 6 (N=5)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematological toxicities										
Thrombocytopenia	9 (39.13)	3 (13.04)	2 (33.3)	1 (16.7)	2 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	2 (40.0)
Leukopenia	1 (4.35)	20 (86.96)	0 (0.0)	5 (83.3)	0 (0.0)	6 (100.0)	1 (16.7)	4 (66.7)	0 (0.0)	5 (100.0)
Anemia	17 (73.91)	2 (8.70)	4 (66.7)	0 (0.0)	5 (83.3)	0 (0.0)	4 (66.7)	1 (16.7)	4 (80.0)	1 (20.0)
Neutropenia	2 (8.70)	19 (82.61)	0 (0.0)	5 (83.3)	0 (0.0)	6 (100.0)	2 (33.3)	3 (50.0)	0 (0.0)	5 (100.0)
Lymphopenia	8 (34.78)	13 (56.52)	2 (33.3)	3 (50.0)	2 (33.3)	3 (50.0)	3 (50.0)	3 (50.0)	1 (20.0)	4 (80.0)
Febrile neutropenia	0 (0.00)	1 (4.35)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Nonhematological toxicities										
Vomiting	10 (43.48)	1 (4.35)	5 (83.3)	0 (0.0)	3 (50.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (20.0)	0 (0.0)
Glutamine transferase increased	12 (52.17)	1 (4.35)	1 (16.7)	0 (0.0)	3 (50.0)	1 (16.7)	3 (50.0)	0 (0.0)	5 (100.0)	0 (0.0)
Alanine aminotransferase increased	6 (26.09)	1 (4.35)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	1 (20.0)
Pulmonary infection	0 (0.00)	1 (4.35)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Nausea	18 (78.26)	0 (0.00)	6 (100.0)	0 (0.0)	5 (83.3)	0 (0.0)	3 (50.0)	0 (0.0)	4 (80.0)	0 (0.0)
Apositia	16 (69.57)	0 (0.00)	5 (83.3)	0 (0.0)	6 (100.0)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)
Asthenia	16 (69.57)	0 (0.00)	6 (100.0)	0 (0.0)	6 (100.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (60.0)	0 (0.0)
Alopecia	15 (65.22)	0 (0.00)	6 (100.0)	0 (0.0)	3 (50.0)	0 (0.0)	4 (66.7)	0 (0.0)	2 (40.0)	0 (0.0)
Vertigo	13 (56.52)	0 (0.00)	5 (83.3)	0 (0.0)	3 (50.0)	0 (0.0)	2 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)
Oral mucositis	12 (52.17)	0 (0.00)	2 (33.3)	0 (0.0)	4 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	4 (80.0)	0 (0.0)
Constipation	12 (52.17)	0 (0.00)	4 (66.7)	0 (0.0)	6 (100.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	10 (43.48)	0 (0.00)	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (60.0)	0 (0.0)
Hypertriglyceridemia	7 (30.43)	0 (0.00)	2 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	2 (40.0)	0 (0.0)
Frequency of urination	6 (26.09)	0 (0.00)	3 (50.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Lactate dehydrogenase elevation	5 (21.74)	0 (0.00)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)

(*Continued*)

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Table 3 (Continued).

Adverse event	All (N=23)		Level 1&2 (N=6)		Level 3&4 (N=6)		Level 5 (N=6)		Level 6 (N=5)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Dysuria	5 (21.74)	0 (0.00)	4 (66.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	5 (21.74)	0 (0.00)	3 (50.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	4 (17.39)	0 (0.00)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)
Hypokalemia	4 (17.39)	0 (0.00)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)
Hyperbilirubinemia	3 (13.04)	0 (0.00)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Hand-foot syndrome	3 (13.04)	0 (0.00)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Pruritus	3 (13.04)	0 (0.00)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperalkaline phosphatase	3 (13.04)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)
Hypoalbuminemia	4 (17.39)	0 (0.00)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)
Aspartate aminotransferase increased	5 (21.74)	0 (0.00)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)
Hematuria	3 (13.04)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (20.0)	0 (0.0)
Weight loss	1 (4.35)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	2 (8.70)	0 (0.00)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Pigment deposition	2 (8.70)	0 (0.00)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cheilitis	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Sore throat	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Urine leukocytosis	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Hyperglycemia	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Cough	1 (4.35)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperuricemia	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Diarrhea	1 (4.35)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	1 (4.35)	0 (0.00)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypochloremia	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
Hypocalcemia	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	1 (4.35)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)

toxicities were also recorded, with nausea experienced by 18 patients (78.26%), anorexia by 16 patients (69.57%), and asthenia also by 16 patients (69.57%), with the majority of these events classified as grade 1–2.

Notably, there were no instances of cardiotoxicity in this study. Oral mucositis occurred in 12 patients, with all cases being mild to moderate (grade 1–2). Hand-foot syndrome (HFS) was reported in three patients, with each case also being mild (grade 1–2). One patient developed grade 3 pneumonia after recovering from myelosuppression. This was an exacerbation of an existing condition related to bronchial obstruction from disease progression, and it was not related to the treatment regimen. There were no deaths related to the treatment throughout the study.

Efficacy

Among the 23 patients who participated in the trial, 12 voluntarily chose to continue receiving treatment with this regimen after consulting with their doctors and completed at least two cycles of PLD+IFO. To preliminarily assess the antitumor efficacy of the treatment regimen, efficacy evaluations were conducted on these 12 patients according to the RECIST 1.1 criteria by independent radiologists. The ORR and disease control rate (DCR) were 33.33% (95% confidence interval (CI): 9.92–65.11) and 83.33% (95% CI: 51.59–97.91), respectively. Among these patients, four (33.33%) achieved a partial response, six (50.00%) exhibited stable disease, and two (16.67%) experienced disease progression, as illustrated in Figure 2.

Additionally, 11 patients received only one cycle of PLD+IFO before switching to other regimens. 7 of these patients changed treatment due to affordability issues, switching to a combination of doxorubicin and IFO. Three patients changed treatment due to disease progression following the initial cycle of chemotherapy. Another patient opted to discontinue the treatment voluntarily.

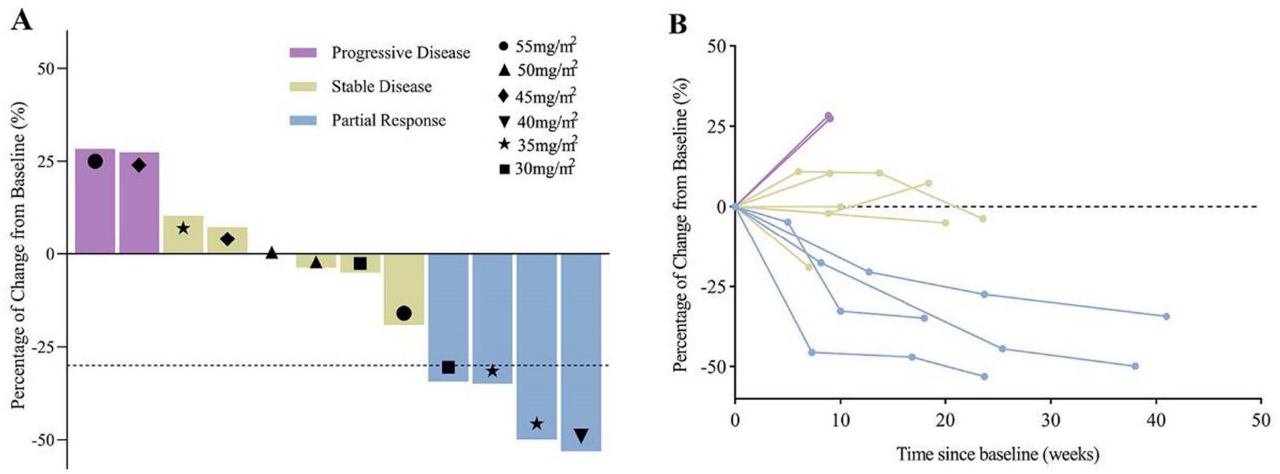

Figure 2 Antitumor activity of pegylated liposomal doxorubicin (PLD) plus ifosfamide (IFO). This figure illustrates the antitumor efficacy of a combination therapy consisting of PLD and IFO, assessed according to RECIST v1.1 criteria. (**A**), The best percentage change from baseline in the sum of the longest diameters of target lesions. This panel visualizes the maximum reduction in tumor size achieved by each patient during the treatment period. (**B**), The longitudinal changes from baseline in the sum of the longest diameters of target lesions over time. This panel tracks the progression or regression of tumor sizes throughout the treatment cycles. The patient cohort (**A** and **B**) includes data from patients who received at least two cycles of PLD+IFO and had at least one post-baseline tumor assessment (n=12).

Discussion

Doxorubicin is one of the most commonly used chemotherapeutic agents in the treatment of STS; however, its clinical utility is often limited by off-target effects. Prodrugs offer a highly promising strategy in targeted cancer therapy by enhancing the selectivity and efficacy of cytotoxic agents. Unlike normal tissues, malignant cells exhibit distinct pathological features, including an acidic tumor microenvironment, expression of tumor-specific antigens, overexpression of certain enzymes or molecules (eg, legumain, acrylic acid), and increased vascular permeability. These characteristics have been exploited in the design of various doxorubicin-based prodrugs to improve targeted drug delivery. Examples include aldoxorubicin,[22] antibody–drug conjugates containing doxorubicin,[23] legubicin,[24] doxorubicin derivatives modified with hydrophobic protecting groups such as 2,6-diisopropyl azidobenzylcarbamate,[25] PLD, and others. Among them, PLD is the most commonly used drug. However, there is no standard recommended dosage, especially in combination chemotherapy.

This phase I trial assessed the MTD of PLD with a fixed dose of IFO and supported by rhG-CSF. We determined the MTD for a single cycle of PLD in combination with IFO (3 g/m^2/day, days 1–3) and rhG-CSF to be 50 mg/m^2. This dosage demonstrated an acceptable safety profile.

Previous phase I studies exploring PLD+IFO for solid tumors established lower MTDs, such as 40 mg/m^2 for STS and 45 mg/m^2 for ovarian cancer, without the addition of rhG-CSF support.[16,26] Our study's higher MTD of 50 mg/m^2 can be attributed to the use of rhG-CSF, which likely mitigated the myelosuppression often associated with chemotherapy, underscoring its utility as a standard support therapy in oncology.[15,27] The variations in MTD across studies may also stem from differences in the treatment cycles evaluated, with our study focusing on the tolerability of a single cycle, unlike other studies that may have considered multiple cycles.

The safety profile served as the secondary endpoint in our study. The EORTC 62012 trial,[10] a multi-center, randomized, phase III study, compared first-line doxorubicin alone against a combination of doxorubicin (75 mg/m^2) and IFO (10 g/m^2) with rhG-CSF support in patients with advanced STS. This trial demonstrated a higher tumor response rate and improved PFS with the combination therapy, but it was also associated with significant toxicity. In the combination arm, the most common severe AEs included grade 3/4 neutropenia (42%), leukopenia (43%), FN (46%), anemia (35%), and thrombocytopenia (33%).

In contrast, our study used PLD instead of doxorubicin, resulting in lower incidences of serious complications. Specifically, the rates of grade 3/4 neutropenia and FN in our study were 82.61% and 4.35%, respectively, indicating a significantly lower rate of FN development compared to the overall rate of severe neutropenia. Additionally, the rates of

anemia and thrombocytopenia were substantially reduced at 8.70% and 13.04%, respectively, compared to 35% and 33% in the EORTC 62012 trial. These findings suggest that the combination of PLD with IFO, as administered in our study, offers a safer alternative to the traditional doxorubicin and IFO combination.

In a related study by Liu et al, PLD (30 mg/m^2 on day 1) was combined with IFO (1.8 g/m^2 from day 1 to day 5) for patients with advanced or metastatic STS as a first-line treatment every 21 days. The primary severe AEs reported included grade 3/4 neutropenia (62.3%), leukopenia (56.5%), anemia (17.4%), and FN (11.6%).[28] Our study, however, observed higher incidences of grade 3/4 neutropenia (82.61% vs 62.3%) and leukopenia (86.96% vs 56.5%). Conversely, the incidences of grade 3/4 anemia (8.7% vs 17.4%) and FN (4.35% vs 11.6%) were lower in our study.

The higher dose range of PLD (30–55 mg/m^2) used in our study, compared to the fixed dose of 30 mg/m^2 in the study by Liu et al, might explain the increased rates of neutropenia and leukopenia. Additionally, anemia, which often manifests as delayed myelotoxicity, tends to occur more frequently after multiple chemotherapy cycles, potentially accounting for the lower incidence of anemia observed in our study. This difference underscores the impacts of the dosage and treatment duration on the safety profile of chemotherapeutic regimens.

Cardiotoxicity is a significant concern limiting the clinical application of anthracyclines, with some cases of cardiotoxicity persisting years after the completion of treatment. Remarkably, no acute cardiotoxicity was observed during the one-cycle study period. Additionally, acute cardiotoxicity was not reported in the 12 patients who completed at least two cycles of PLD+IFO, mainly due to the structural modifications in PLD. However, long-term cardiac toxicity could not be assessed in this study. The encapsulation of doxorubicin in liposomes leads to reduced cardiac uptake due to the enhanced permeability and retention effect of the liposome's macromolecular structure. A preclinical study has confirmed that liposomal encapsulation diminishes cardiac absorption compared to conventional doxorubicin.[29] PLD primarily accumulates in the liver and spleen, owing to the enrichment of macrophages in the liver and spleen but not in heart tissue,[28] distinguishing its safety profile from that of doxorubicin, which has a well-defined cumulative lifetime dose upper limit for cardiotoxicity that is generally 450–550 mg/m^2. In contrast, no established cumulative dose upper limit exists for PLD, as evidenced by reports of patients continuing PLD therapy beyond a median dose of 1680 mg/m^2.[30]

HFS and oral mucositis are notable side effects specifically associated with the use of PLD.[31–33] These conditions arise from the release of doxorubicin and metal ions in the skin, leading to the generation of reactive oxygen species that cause dysfunction in keratinocytes and trigger an inflammatory response.[34,35] Oral mucositis emerged as the major DLT when a single cycle of PLD administration reached 80 mg/m^2. When PLD was administered at a dose of 60 mg/m^2 every three weeks, HFS became the primary DLT after more than three chemotherapy cycles, with an incidence of 100% (4/4).[31]

In our study, which involved a single cycle of PLD at the established MTD of 50 mg/m^2 in combination with IFO, both HFS and oral mucositis were observed but remained mild, graded as 1 or 2. Additionally, among the 12 patients receiving at least two cycles of PLD+IFO, we did not observe any dose-limiting toxicities related to HFS or oral mucositis. However, in our study, patients received a maximum of six cycles of this regimen according to the clinical guidelines, and it remains unclear whether an increased number of cycles would result in these specific side effects. Further research is needed to ascertain the long-term impact of extended PLD therapy on the incidence of HFS and oral mucositis.

Among the 23 patients who participated in this trial, 12 voluntarily chose to continue to receive treatment with this regimen after consulting with their doctors, and they completed at least two cycles of PLD+IFO. The ORR observed was 33.33%. Notably, six patients chose to continue the PLD+IFO treatment beyond four cycles, with four achieving a partial response, including one patient who reached a partial response after two cycles and two patients after four cycles, suggesting enhanced efficacy with prolonged treatment and indicating the regimen's potential for long-term use.

In comparison, Liu et al have reported an ORR of 26.1% and a DCR of 81.2%, which align closely with the results from the doxorubicin plus IFO arm of the EORTC 62012 trial, where the ORR and DCR were 26% and 77%, respectively.[10] These findings suggest that PLD can match the efficacy of doxorubicin while potentially offering a reduced toxicity profile.[10] This could position PLD+IFO as a viable alternative for the treatment of advanced STS, promising comparable therapeutic benefits with possibly fewer adverse effects.

In this study, we confirmed that the MTD of PLD combined with a fixed dose of IFO (3 g/m^2/day, days 1–3) and supported by rhG-CSF is 50 mg/m^2. This dosage demonstrated a tolerable AE profile, bolstering our confidence for utilizing higher doses of PLD for the clinical treatment of STS to potentially enhance therapeutic efficacy.

However, this study had several limitations. We primarily focused on determining the MTD and evaluating the safety of a single cycle of the PLD+IFO regimen. The safety and tolerability of administering multiple cycles, which is critical for long-term treatment strategies, require further investigation. The implications of prolonged treatment, particularly regarding cumulative toxicity and patient tolerance over successive cycles, remain to be fully explored.

Conclusion

In conclusion, we determined that the MTD of PLD combined with IFO (3 g/m^2/day, days 1–3) and supported by rhG-CSF for patients with localized unresectable, advanced, or metastatic STS is 50 mg/m^2. This regimen demonstrated a tolerable safety profile and promising efficacy, indicating potential benefits for patients with advanced STS. However, these preliminary findings necessitate further research to validate the efficacy and safety of this treatment over multiple cycles and to explore the full therapeutic potential of the regimen in this patient population.

Abbreviations

AEs, adverse events; CI, confidence interval; DCR, disease control rate; DLT, dose-limiting toxicities; ECOG, Eastern Cooperative Oncology Group; FN, febrile neutropenia; HFS, hand-foot syndrome; IFO, ifosfamide; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PLD, pegylated liposomal doxorubicin; PS, performance status; rhG-CSF, recombinant human granulocyte colony-stimulating factor; STS, soft tissue sarcoma.

Data Sharing Statement

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This phase I, single-center, dose-escalation study received approval from the Clinical Trial Ethics Committee of Huazhong University of Science and Technology, with ethics approval number [2019] (25)-2. Prior to participation, all subjects gave written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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