Non-pegylated Liposomal Doxorubicin plus Ifosfamide in Metastatic Soft Tissue Sarcoma: Results from a Phase-II Trial

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Abstract. *Background/Aim: Non-pegylated liposomal doxorubicin (NPLD) has demonstrated antitumour activity equivalent to conventional doxorubicin and a significantly lower risk of cardiotoxicity. This phase II trial was performed to evaluate the activity and the safety of NPLD and ifosfamide combination in patients with metastatic soft tissue sarcoma. Patients and Methods: Thirty-four patients received NPLD 40 mg/m^2 (d1) and ifosfamide 3 g/m^2/day (d1-3) every three weeks as first-line therapy of metastatic soft tissue sarcoma. The treatment was planned for a maximum of six cycles. Results: The objective response (OR) rate among response-assessable patients was 55.9%. The median progression-free survival (PFS) was 4.2 months and the median overall survival (OS) was 11.2 months. Symptomatic grade 3 cardiotoxicity occurred in one patient (3%). Conclusion: The combination of NPLD and ifosfamide reported in a population of metastatic soft tissue sarcoma patients at risk for developing heart failure encourage antitumour activity, similar to that of classical doxorubicin.*

Soft tissue sarcomas (STS) are rare heterogeneous mesenchymal neoplasms accounting for less than 1% of adult malignancies. Doxorubicin-plus-ifosfamide remains the 'gold standard' for the treatment of advanced STS (1-3).

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Alternative drugs, such as trabectedin, gemcitabine, taxanes and dacarbazine, are currently employed but none of them was shown to be superior compared to anthracyclines (1, 2, 4). However, major responses have been reported in peculiar histologies, such as trabectedin in myxoid liposarcoma, paclitaxel in angiosarcoma and high-dose ifosfamide in synoval sarcoma, respectively (5-7).

Unfortunately, doxorubicin is associated with cumulative and irreversible myocardial toxicity (8), resulting in cardiomyopathy in 1-10% of patients receiving a total dose of more than 550 mg/m^2 (9-13). Therefore, strategies to reduce cardiotoxicity have been developed consisting of different schedules (*i.e.*, converting bolus injections of anthracycline into prolonged infusions) (14) or use of cardioprotective agents, such as the iron-chelating agent dexrazoxane (15). However, results have been disappointing (14, 16).

Furthermore, anthracycline analogues, such as epirubicin, which has lower cardiotoxicity, and pegylated formulations have been developed. Formulations of doxorubicin encapsulated in liposomes show decreased accumulation in tissues with tight junctions, such as the heart, and higher uptake by the fenestrated microvasculature of tumour tissue (17-21).

A non-pegylated liposomal-encapsulated doxorubicin (NPLD) (22-24) demonstrated equivalent antitumor activity and significantly lowered cardiotoxicity and grade 4 neutropenia (18, 25), compared to doxorubicin, in phase II and III studies in metastatic breast cancer patients. In addition, NPLD has a favourable tolerability profile in terms of hematological, mucosal and gastrointestinal toxicities (10, 17).

In a previous phase I study, we determined the maximum tolerated dose (MTD) of NPLD in combination with ifosfamide (26). Herein, we present the results of a phase II trial of NPLD 40 mg/m^2 (day 1) in combination with

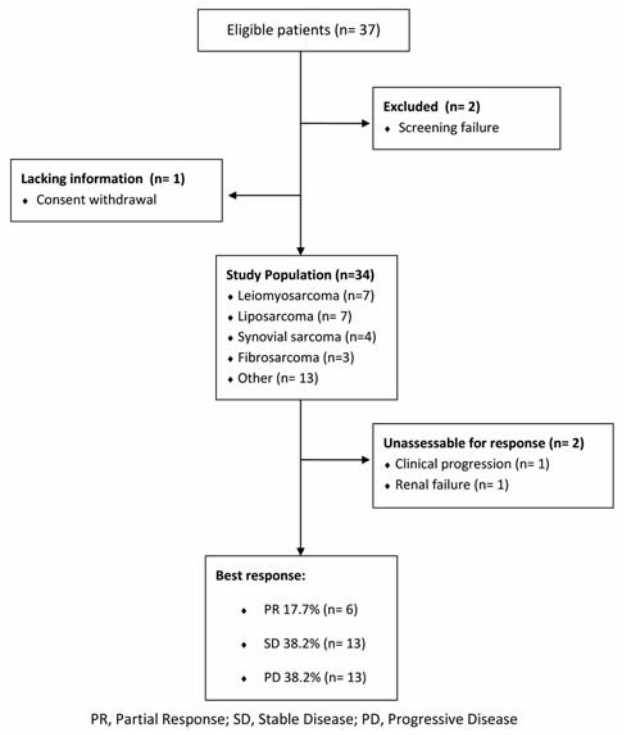

Figure 1. *CONSORT flow diagram.*

ifosfamide 3,000 mg/m^2 (day 1-3) every three weeks in patients with metastatic and advanced STS.

Patients and Methods

Patients. The present study was a multicenter prospective phase II trial (ONC-2005-001). Eligibility criteria were: histological diagnosis of STS, either metastatic or relapsed within 6 months from a previous adjuvant treatment; age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status score ≤2; life expectancy ≥3 months; measurable disease. All patients were required to have absolute neutrophils ≥1.5×10^9/l and platelets ≥100×10^9/l; a serum creatinine concentration ≤1.6 mg/dl or a creatinine clearance (estimated using the Cockroft-Gault formula) ≥60 ml/min; a serum bilirubin concentration <1.5 mg/dl; serum alkaline phosphatase, AST and ALT ≤2.5 × the upper limit of normal values (in case of liver metastases ≤5 × the upper limit of normal values); cardiac ejection fraction ≥50% as determined by echocardiography; a minimum interval of four weeks from previous radiotherapy. Exclusion criteria were: prior cumulative doxorubicin dose ≥300 mg/m^2 or epirubicin dose ≥450 mg/m^2; evidence of brain or meningeal metastases; previous or concomitant malignant disease, with the exception of cervical carcinoma *in situ* and cutaneous spinocellular carcinoma; uncontrolled severe infections; lack of adequate effective contraception in women of fertile age; antitumor treatment within four weeks of enrolment; inadequate patient compliance.

Table I. *Baseline characteristics of the 34 evaluable patients.*

Characteristic	N (%)/median (range)
Age	52 (28-77)
Gender	
Male	17 (50%)
Female	17 (50%)
Histotype	
Leyomiosarcoma	7 (20.6)
Liposarcoma	7 (20.6)
Synovial sarcoma	4 (11.8)
Fibrosarcoma	3 (8.8)
Other	13 (38.2)
Previous chemotherapy	
No	29 (85)
Yes	5 (15)
- Anthracycline-based	3 (9)

The study was performed in accordance with the Declaration of Helsinki and local ethics regulations. Written informed consent was obtained from all patients prior to study entry.

Study design and treatment. We designed a phase II study of NPLD 40 mg/m^2 (day 1) associated with ifosfamide 3,000 mg/m^2 (day 1-3) every three weeks in metastatic or recurrent STS. Subcutaneous granulocyte colony stimulating factor (G-CSF) was administered from day +7 to day +12 following each cycle of treatment.

The primary objective was to evaluate the activity of NPLD-ifosfamide in terms of objective response rate (ORR), calculated as the sum of complete response (CR), partial response (PR) and stable disease (SD). A single arm one step phase II Fleming design was planned, considering a p0 <25% representative of an inactive treatment, while a p1 value of 50% as a promising one, with a statistically significance level α of 0.05 (one-side) and a power of 90% (β=0.10). This hypothesis required that a total of 32 patients with at least one cycle of chemotherapy had to be enrolled and at least 13 objective responses had to be observed. Response to treatment was assessed every two cycles according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.0.

Secondary endpoints were progression-free survival (PFS), overall survival (OS) and toxicity.

Data were summarized as frequencies and proportions or as median and range, when appropriate. Survival analyses were performed using the Kaplan-Meier method.

Results

In order to obtain 32 patients evaluable for response, a total of 37 patients with metastatic or recurrent unresectable STS were enrolled between September 2006 and November 2009. Out of these, 2 patients dropped-out of the study due to screening failure and one withdrew the informed consent. A CONSORT flow diagram for patients enrolled in the study is represented in Figure 1. Baseline characteristics of the remaining 34 patients are summarized in Table I. The median

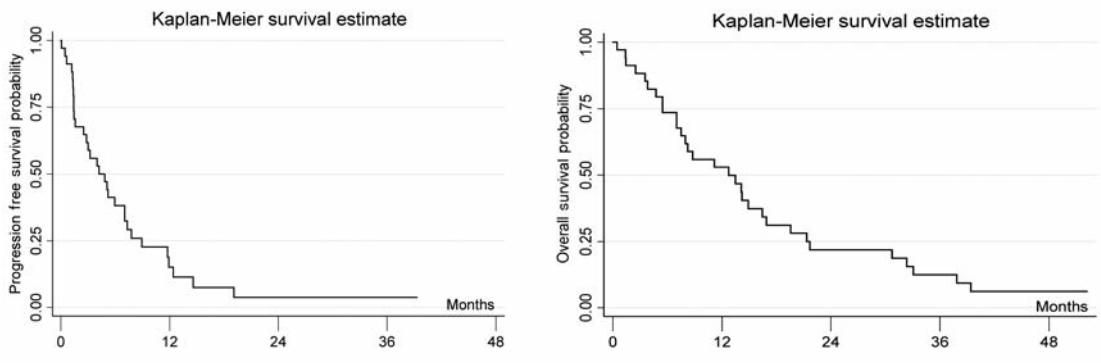

Figure 2. *Progression-free and overall survival.*

Table II. *Severe adverse events (SAEs): three patients reported two SAEs respectively (cardiac failure and atrial fibrillation; dyspnoea and dyspnoea due to PD; dehydratation and acute renal failure).*

Patient	SAE	Grade	Severity	Drug-related	Outcome
30	Thoracic pain	3	Hospitalization	Possible	Recovery
9	Atrial fibrillation	3	Hospitalization	Uncertain	Worsening
9	Cardiac failure	3	Death	Uncertain	Death
16	Dyspnoea	3	Hospitalization	No	Recovery with sequelae
16	Dyspnoea due to PD	3	Death	No	Death
92	Dehydratation	2	Hospitalization	Probable	Recovery with sequelae
92	Acute renal failure	2	Hospitalization	Probable	Recovery with sequelae

PD, Progressive disease.

age was 52 years (range=28-77 years) and male/female ratio was 1:1. Leiomyosarcoma (n=7, 20.6%) and liposarcoma (n=7, 20.6%) were the most frequent histological subtypes followed by synovial sarcoma (n=4, 11.8%) and fibrosarcoma (n=3, 8.8%). Five out of 34 patients were pre-treated; three of these patients had received anthracyclines with a maximum cumulative dose of 150 mg/m^2.

Response evaluation. All enrolled patients received at least one dose of chemotherapy. The primary end-point was satisfying, reporting a total of 19 objective responses in the entire population, with an ORR of 55.9% (19/34 patients). The best responses according to RECIST v1.0 were: PR in 6 (17.7%), SD in 13 (38.2%), progressive disease (PD) in 13 patients (38.2%) and in 2 (5.9%) not evaluable, respectively. These two patients interrupted chemotherapy early after 2 and 3 days, respectively, due to renal failure and worsening clinical conditions and, therefore, did not undergo a re-evaluation CT scan.

Survival analysis. Among the 34 enrolled patients, we observed a median PFS of 4.2 months and a median OS of 12.7 months (Figure 2). The 6-month rate of PFS and OS was 38.2 and 73.5%, respectively. One-year PFS was 15.1% and 1 and 2-year OS were 52.9 and 21.8%, respectively.

Safety. Twenty-four patients experienced one or more adverse events (AEs). A total of 74 AEs were observed: 30 (40.5%) of grade 1 and 35 (42.3%) of grade 2. Grade 3 not severe AEs included anemia (1/34 patients; 3%), febrile neutropenia (3%), prothrombin time reduction (3%) and thrombocytopenia (3%).

Seven severe AEs (SAEs) were recorded: one possible (thoracic pain) and two probable (dehydratation and acute renal failure) drug-correlated. Table II summarizes all observed SAEs in our study population. In particular, grade 3 atrial fibrillation and cardiac failure and consequent fatal acute pulmonary edema occurred in one patient three days after the first dose of NPLD was defined by the investigator as not certainly related to the study drug.

Discussion

The present phase II study was performed to establish the activity and the safety of NPLD in combination with ifosfamide in front-line treatment of advanced or metastatic

STS. Liposomal doxorubicin has been used in Kaposi's sarcoma with favourable results. However, in advanced/metastatic STS some reports showed a modest activity in first- or later-line therapy with no PFS or OS improvement than historical series (27-29).

No data on NPLD use in STS have been reported so far. In our study, the combination regimen of NPLD with ifosfamide showed an ORR of 55.9%, which attained the pre-specified primary endpoint. These results are similar to those reported in trials assessing doxorubicin-ifosfamide combinations in first-line therapy for metastatic disease (30, 31).

Haematological and non-haematological non-cardiac adverse events occurred at expected rates, similar to those observed in the conventional doxorubicin-plus-ifosfamide combination.

One patient (3%) with no prior exposure to anthracyclines experienced two subsequent grade 3 symptomatic cardiac toxicities (atrial fibrillation and acute congestive heart failure). Different factors, such as cumulative dose of anthracyclines, age, pre-existing cardiac dysfunction and long-standing hypertension, could increase the risk of cardiotoxicity. In our study, neither prior anthracyclines cumulative-dose exposure nor initial cardiac dysfunction could explain the reported events. However, our patient had a rapidly progressing mediastinal mass causing superior vena cava and tracheal compression. While no change in hemodynamic parameters was recorded before starting chemotherapy, we hypothesize that mediastinal involvement with hyperhydration schedule for ifosfamide infusion could be responsible for the sudden cardiac failure we observed in our patient. At present, there is no contraindication for the use of anthracyclines in patients with mediastinal mass. Some reports have demonstrated safe anthracycline administration for mediastinal disease (33) even if most of them were conducted in different settings (adjuvant therapy after surgery, minor mediastinal involvement, concomitant radiation therapy (34-36)). On the base of this case, we suggest a careful basal evaluation and a strict heart activity monitoring in patients with extensive mediastinal involvement undergoing combination treatment with anthracycline and ifosfamide.

Survival analysis showed a median PFS and OS of 4.2 and 11.2 months, respectively, and a 6-month PFS rate of 38.2%. Therefore, according to Van Glabbeke criteria for front-line therapy (32), the proposed chemotherapy regimen with NPLD is of valuable activity in advanced STS regardless of specific histologies.

In conclusion, we observed that the substitution of anthracyclines with NPLD in combination with ifosfamide induces comparable results in terms of response and outcome. Despite the single observed case of cardiotoxicity in our series and considering the clearly demonstrated better cardiotoxicity profile of NPLD versus doxorubicin in other trials, we suggest the use of NPLD-ifosfamide regimen in adult patients with advanced STS at risk for developing heart failure.

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