RESEARCH ARTICLE

Comparison of Efficacy and Toxicity of First Line Chemotherapy with or without Epirubicin for Patients with Advanced Stage Soft Tissue Sarcoma

Jie Cao, Xin-En Huang*, Jin Liu, Xue-Yan Wu, Yan-Yan Lu

Abstract

Purpose: To compare the safety and efficacy of first-line chemotherapy regimen with or without doxorubicin in treating patients with advanced soft tissue sarcoma (STS). Patients and Methods: We retrospectively analyzed a cohort of 56 patients histologically confirmed with STS who were treated at Jiangsu Cancer Hospital and Research Institute from July 2011 to June 2012.The basic element of first line chemotherapy contained epirubicin in group B and lacked epirubicin in group A. Response was assessed using RECIST criteria. The Kaplan-Meier method was used to estimate progress free survival (PFS). Results: According to RECIST criteria , patients in group treated by chemotherapy without epirubicin, the objective response (OR) ratio was 6.5 % (CR0%+PR6.5%). Disease control rate (DCR=CR+PR+SD) was 25.8% with a median follow-up of 14.6 months, including 2 patients achieving a partial response (PR 6.5%) and a stable response (SD 19.4%) in 6. In group B with epirubicin based regimens, no patient had complete response, PR (28 %) was observed in 7 and SD (24 %) in 6. DCR was observed in 13 patients (52%). By Fisher's exact test, the DCR difference between the two groups was statistically significant (p=0.046). In group A, median PFS was 3.0 months (95%CI:2.1-3.8), compared with 4.0 months (95% CI:3.03-4.97) in group B (p=0.0397 by log-rank test). Epirubicin based chemotherapy and ECOG performance status 0-1 were identified as favorable factors for progression in our cohort of patients. Differences of nonhematologic and hematologic toxicities were not statistically significant between the two groups, and the addition of epirobicin was not associated with cardiac toxicity (p=0.446). Conclusion: Our study demonstrates that epirubicin-based chemotherapy is effective and well tolerated, and is superior to chemotherapy without epirubicin regarding efficacy. Therefore it is recommended that epirubicin-based chemotherapy should be considered as first line for patients with advanced STS.

Keywords: First line chemotherapy - doxorubicin - advanced stage soft tissue sarcoma - epirubicin

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Introduction

Soft tissue sarcomas (STSs) are relatively rare and heterogeneous originating from connective cell with distinct clinical and pathological features. Systemic chemotherapy given with palliative intent is the only available treatment option for many patients with locally advanced unresectable and metastatic STS, yet the results are generally unsatisfactory, few patients experiencing long-term survival (Mocellin et al., 2006). Doxorubicin, first reported to have activity in sarcomas 40 years ago, remains an important first-line treatment of choice for many subtypes, Single -agent doxorubicin is the most widely accepted treatment option for these tumors (Sleijfer et al., 2005). Advanced and metastatic STSs are currently treated by doxorubicin and / or ifosfamide-based regimens at first line ,with an objective response (OR) of 23% to 48% (Maurel et al., 2009). And the rarity and diverse characteristics of sarcomas has impeded the development of new treatments. It is now recognized that the choice of chemotherapy may be adapted to the site of the disease and histological or molecular subtype (Krikelis et al., 2010). Other cytotoxic agents, such as paclitaxel for angiosarcoma or gemcitabine with docetaxel forleiomyosarcoma, are commonly used for certain histologic subtypes based on relatively small studies (Maki et al., 2007; Duffaud et al., 2008; Schlemmer et al., 2008). More and more other cytotoxic agents combined with doxorubicin are practiced on advanced STSs patients, and reported to produce higher tumor response rates, mainly in single-center studies of selected patients, however randomized trials failed to detect a survival benefit for these combinations (Santoro,et al,1995. Antman et al., 1993.Edmonson et al., 1993)or intensified chemotherapy regimens (Le Cesne et al., 2000; Worden et al., 2005).

Doxorubicin is linked with cumulative cardiotoxicity.

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Table 1. Main Characteristics of Patients

Patient characteristics	Group A N	Group B N	Total
Gender			
Male	19	22	41
Female	12	3	15
Age			
Median age at enrollment	42.7	45.6	44
Age at registration	8-67	21-75	8-75
≤40	12	6	18
>40, ≤60	14	17	31
>60	5	2	7
Histology			
Osteosarcoma	4	3	7
Chondrosarcoma	1	1	2
Hemangioendothelioma	1	2	3
Rhabdomyosarcoma	8	6	14
Leiomyosarcoma	1	4	5
Synovial sarcoma	2	2	4
Stromal sarcoma	7	3	10
Myofibrosarcoma	2	1	3
Liposarcoma	1	2	3
Carcinosarcoma	3	1	4
Undifferentiated sarcoma	1	0	1
Radiotherapy			
Yes	11	12	23
No	20	13	33
Radical surgery			
Yes	13	9	22
No	18	16	34
ECOG performance status			
0-1	21	20	41
>2	10	5	15
Bone Metastasis			
Yes	4	7	11
No	27	18	45
Organ Metastasis			
Yes	20	13	33
No	11	12	23
Histopathological grade			
Grade I-II	18	14	32
Grade III-IV	13	11	24

Group A, patients treated by chemotherapy without epirubicin; Group B, patients treated by epirubicin-based chemotherapy

It is important to develop regimens of anthracycline analogues with potentially less toxicity and equal or better activity. In a randomized study comparing doxorubicin and epirubicin both at a dose of 75 mg /m2 ,no difference in survival and duration of response was found, and the response rate was only slightly in favor of doxorubicin (Mouridsen et al., 1987). These data indicate that epirubicin may be less toxic than doxorubicin when administered in equivalent dosage.

At present, few studies specifically compared the safety and efficacy of first line chemotherapy with or without epirubicin for patients with advanced STS. The background prompted us to retrospectively conducted this study with the aim to investigate the role of routine palliative chemotherapy in a cohort of patients with advanced STS treated at JiangSu Cancer Hospital & Research Institute. We aim to analyze the safety and efficacy outcome of STS patients treated by first line regimens with or without epirubicin, and to identify the prognostic factors that will predict which patients are most likely to derive benefit from this treatment.

Materials and Methods

Patient selection

The medical records of patients who received chemotherapy at JiangSu Cancer Hospital & Research Institute from July 2011 to June 2012 with recurrent or advanced (metastatic or nonresectable) measurable STS (Table 1), were retrospectively reviewed. Advanced disease was defined as primary tumor or local recurrence not amenable to complete surgical resection, or the presence of metastatic disease. Tissue diagnosis of STS was confirmed in each case independently by two pathologists. Patients with the chemo sensitive subtypes Ewing sarcoma, rhabdomyosarcoma, and desmoplastic small round cell tumor, as well as those with gastrointestinal stromal tumors (GIST), were excluded from this study. Patients who received adjuvant chemotherapy were only included in the analysis if they subsequently received chemotherapy for recurrent or metastatic disease. Additional information extracted from clinical records included: sex, age ,pathology subtypes, histopathological grade, organ of metastasis, eastern cooperative oncology group (ECOG) performance status ,site of metastases or local recurrence; chemotherapy dosage and schedule used, number of courses administered, and response to treatment; radiotherapy administration; and metastasectomy.

Treatment

Patients in this retrospective review were treated by combined chemotherapy regimens as first line for two to six cycles, with or without epirubicin. Epirubicin was injected 60 mg/m^2 intravenously by bolus on days 1 of a 21 day cycle. The other agents included one or two combinations of ifosfamide (6 mg/m^2 given divided for 5 days), paclitaxel (175 mg/m^2 as an intravenous infusion over 3h), gemcitabine (1000 mg/m^2 infused for day 1 and day 8), dacarbazine (200 mg/m^2 infused daily from day 1 to day 5), cisplstin (75 mg/m^2 in divided doses of 25 mg/m^2 infused daily for 3 day). Cycles were repeated every 21 to 28 days. The reasons for discontinuation of treatment contained no-tolerance of chemotherapy toxicities, disease progression, or patients personal reason .

Efficacy and Toxicity evaluation

The primary end point was objective response rate (OR) and secondary end points were progress free survival (PFS) and toxicity. PFS was defined as the time from first treatments until clinical or radiographic progression, or death. RR was reported on an intent-to-treat basis. Best overall response was recorded from the start of treatment until disease progression. Baseline and follow-up imaging were performed with CT and/or MRI every two cycles to assess response. Demographic data of response to chemotherapy was recorded by retrospective reviewing of radiology reports. All imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI) scans, were reviewed by radiologist, and radiographic studies reassessed and responses were classified (complete

Table 2. Efficacy of Two Groups

	Group A N(%)	Group B N(%)	*p* value
Efficacy			
CR	0	0	
PR	2(6.5%)	7(28%)	
SD	6(19.4%)	6(24%)	
DCR	25 (25.8%)	13(52%)	0.046
PD	23(74.2%)	12(48%)	
Survival Analysis			
Median PFS	3.0m	4.0m	
95%CI	2.11-3.8m	3.03-4.97m	0.039

DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

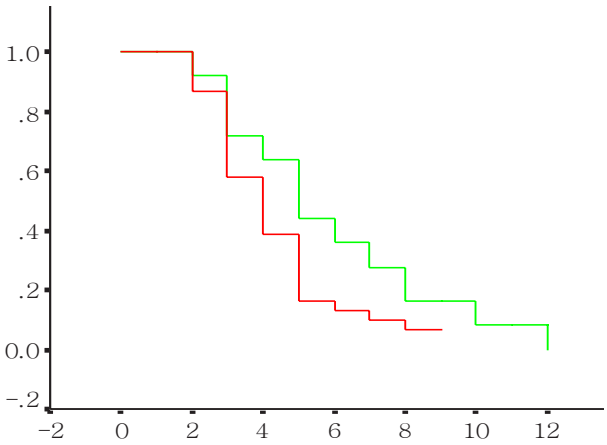

Figure 1. Percent of Progress Free Kaplan-Meier (PFS) Analysis According to Chemotherapy (vertical axis: percent of progress free survival; horizontal axis:time of months). red line: Group A (patients treated by chemotherapy without epirubicin); blue line: GroupB (patients treated by epirubicin-based chemotherapy) (*P*=0.039)

response CR, partial response PR, stable disease SD, progressive disease PD, and not evaluated) according to the response evaluation criteria in solid tumors (RECIST) (Eisenhauer et al., 2009). Response was assessed every two to three cycles. Follow-up was performed at 3 monthly intervals following the end of treatment. All patients were analyzed for efficacy on an intention-to-treat basis.

Toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. (NCI CTC 2003) Toxicity data (dose reduction, discontinuation of chemotherapy, and death during treatment) were gathered. Patients receiving at least one cycle of chemotherapy were analyzed for toxicity. All adverse events resulting in discontinuation of study were followed closely until resolution or stabilization.

Statistical analysis and research experience

Fishers extact test was used to determine the association of response and categorical variables, as well as to compare some patient characteristics between two groups. Kaplan-Meier method and log-rank test were used to analyze time-to-event variables, including progression -free survival. Differences in survival between subgroups were compared using log-rank test. A step-up procedure was used and variables were entered at the 5% level of significance. Hazard ratios (HRs) were calculated together with their 95% confidence intervals (CIs).

The variables were investigated as potential prognostic factors for PFS by means of a univariate log-rank analysis. The independent significance of variables was assessed in a multivariate Cox regression analyses. Data analysis was performed using SPSS version 19.0.

We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Liu et al., 2012; Shu et al., 2012; Xu et al., 2012; Xu et al., 2012; Yu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Zhang et al., 2012; Chen et al., 2013; Dai et al., 2013; Deng et al., 2013; Gu et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Sun et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

Patient characteristics

Between July 2011 to June 2012, a cohort of 56 patients histologically confirmed with advanced STS, and were treated by first line chemotherapy at Jiangsu Cancer Hospital &Research Institute. Patient characteristics are shown in Table 1.

In group A , 31 patients were treated by chemotherapy without epirubicin ,in group B ,25 were treated by epirubicin based regimens. Male-to-female ratio was 34/22 and the median age was 44 years (range; 8-75 years).The median age of group A was 42.7 years (range; 8-67 years); the median age of group B was 45.6 years (range; 21-75 years). Median ECOG PS was 1 (range, 0–2). 39 percent of the patients had undergone complete surgical excision of primary disease, while 41 percent had received postsurgical radiotherapy. The most prevalent histologic subtype was rhabdomyosarcoma (25%),stromal sarcoma (18%), osteosarcoma (12.5%) , followed by leiomyosarcoma, carcinosarcoma, synovial sarcoma , liposarcoma, hemangioendothelioma, etc. The median follow-up time was 14.6 months. A total of 165 cycles of chemotherapy were administered, the median number of cycle was 2.96 (range;1-8).

Efficacy

According to RECIST criteria, in group A of patients treated by chemotherapy without epirubicin, OR ratio was 6.5 % (CR0%+PR6.5%). Including 2 patients achieved PR (6.5%), and SD (19.4%) in 6, disease control rate (DCR=CR+PR+SD) was observed in 8 (25.8%) with a median follow-up of 14.6 months. In group B with epirubicin based regimens, no patient had complete response, PR (28%) was observed in 7 patients and SD (24%) in 6 patients. DCR was observed in 13 patients (52%). In both groups no CR was observed. By Fisher's exact test, patients in group B demonstrated a significantly higher rate of DCR, the difference of DCR between two groups is statistical significant (*P*=0.046) (Table 2).

Table 3. WHO Grades 3/4 Treatment-related Toxicity for Two Groups

Toxicity	Group A		Group B		*P* value
	N	%	N	%	<0.05
Haematological toxicity					
Anaemia	4	12.9	3	12.0	0.623
Leukopenia	11	35.4	12	48.0	0.417
Neutropenia	8	25.8	4	16.0	0.516
Thrombocytopenia	4	12.9	2	8.0	0.682
Non-haernatological toxicity					
Nausea/vomiting	8	25.8	10	40.0	0.388
Peripheral neuropathy	4	12.9	5	25.0	0.493
Infection	5	16.1	4	16.0	0.648
Mucostis	7	22.5	6	24.0	0.587
Cardiotoxicity	0	0	1	0	0.446

Table 4. Multivariate Analysis: Identification of Independent Prognostic Factor(s)

Covariets	Adjusted hazard	95%confidence intervals	*P* (<0.05)
Gender	0.83	0.40-1.69	0.605
Age >40, ≤60	1.05	0.41-2.72	0.920
Age >60	0.58	0.23-1.47	0.249
Radiotherapy	0.89	0.44-1.79	0.737
Radical surgery	0.58	0.29-1.15	0.121
Chemotherapy regimens	1.97	0.91-4.27	0.019
ECOG performance status	0.43	0.20-0.91	0.028
Bone Metastasis	0.66	0.29-1.46	0.299
Main Organ Metastasis	1.73	0.83-3.64	0.146
Histopathological grade	1.09	0.59-1.99	0.783

Survival analysis

In group A, median PFS was 3.0 months (95% CI:2.1-3.8), compared with 4.0 months (95% CI:3.03-4.97) in group B. By log-rank test, *p* value of the differences in PFS between two groups were 0.0397 (<0.05) (Figure 1).

Prognostic factor analysis

Based on previous report , predictive factors of progression after commencement of first line chemotherapy for advanced STS include gender, age, histology subtypes, radiotherapy, radical surgery, ECOG performance status, bone metastasis ,main internal organ metastasis (brain, lung, liver), histopathological grade (Vasilios Karavasilis et al., 2008; Kroep et al., 2011; Penel et al., 2012).

By Cox model of multivariate analysis on predictive factors, treatment was a strong independent prognostic factor, patients who received not anthracyclines regimen tended to have a worse PFS (compared with anthracycline based chemotherapy, HR=1.97, 95%CI 0.91-4.27, *P*=0.019). In addition to treatment, the PS was another independent prognostic factors. ECOG performance status 0-1 was found to be independent optimistic prognostic factor (HR= 0.43, 95% CI: 0.20-0.91, *P* 0.028 < 0.05). After adjusting for other factors, ECOG performance status was still statistically significant on PFS, with a median of 4.35 months in ECOG 0-1 and 2.56 months in ECOG≥2. By log-rank test, p value for the differences in PFS was 0.022 (Figure 2). The risk of progression increased with an increase in the performance status to the next highest score .Results of the multivariate analysis for PFS are described in Table 4.

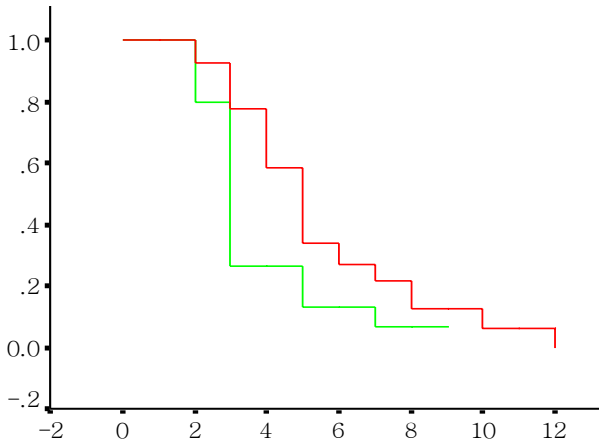

Figure 2. Percent of Progress Free Kaplan-Meier (PFS) Survival Analysis by Performance Status. red line: patients performance status ECOG 0-1; blue line: patients performance status ECOG≥2 (*P*=0.022)

Tocicities

All patients treated by at least one cycle of chemotherapy were analysed for toxicities. In two groups, the most common nonhematologic toxicities consisted of nausea/vomiting, mucositis, peripheral neuropathy, and infection. WHO grade 3-4 haematological toxicities included leukopenia, neutropenia, anaemia and thrombocytopenia. Detailed toxicities classified according to NCI CTC criteria are presented in Table 4. The differences of none hematologic and hematologic toxicities were not statistically significant in two groups (*P*>0.05).In group B, only one patient reported cardiac ejection rate (LVEF) decreased from 65% to 20% after eight cycles, but the difference between two groups is not statistically signigicant (*P*=0.446). Treatment for all patients the patients was generally well tolerated. According to medical records, 9 patients (16%) needed a dose reduction due to intolerability to grade 3-4 toxicities. No patient discontinued treatment due to toxicity or died of treatment-related toxicities.

Discussion

Although with heterogeneity and acknowledged clinical, pathologic, and molecular differences, STS are generally treated in a similar fashion. Palliative chemotherapy is considered the only therapeutic option for patients with advanced STS which not amenable to surgery or radiotherapy (Clark et al., 2005).

Doxorubicin remains the best single agent with proven activity, providing a response rate of 15%–35% in metastatic soft tissue sarcoma whatever the histological subtypes (Sleijfer et al., 2005). In EORTC 61012 trial, with 455 locally advanced STS, after a median follow-up of 56 months ,Professor Graaf concluded that doxorubicin/ifosfamide compared with doxorubicin alone was associated with no significant difference in overall survival (OS) but with a longer PFS (median: 7.4 m versus 4.6 m; HR 0.74; 95% CI: 0.60-0.90, *p*=0.003) and higher overall

response rate (26.5% versus 13.6%), but this was at the cost of increased toxicity. that the lack of a significant improvement in OS means that the routine use of this intensive combination of doxorubicin and ifosfamide is not supported, the standard treatment remains single-agent doxorubicin (Van der Graaf et al., 2012). Guidelines recommend first-line anthracycline-based (with or without ifosfamide)chemotherapy as the standard of care for mSTS patients, with trabectedin, gemcitabine with or without docetaxel, and dacarbazine reserved for second or later lines of treatment (Casali et al., 2010; Grimer et al., 2010; NCCN, 2011).

In our study, epirubicin-based regimens provide a response rate of 28%, DCR 48%, and a median PFS 4.0 months. These results are concordant with previous results. It is reported that the median progression-free survival is 3.7 months with doxorubicin alone and 5.4 months with doxorubicin plus ifosfamide combination (Fury et al., 2005), doxorubicin- or ifosfamide- based regimens provide objective response in 7 out of 17 assessable patients (26%) (Fayette et al., 2007). There is data that 45% of 488 mSTS patients derived clinical benefit from first-line palliative chemotherapy (Karavasilis et al., 2008). Our study highlighted that epirubicin may have comparative efficacy with doxorubicin when administered in equivalent doses.

However, no comparative study has reported a survival advantage for patients treated with epirubicin based chemotherapy compared with those without epirubicin. In our study, it is statistical significant that the epirubicin based chemotherapy regimens improved the DCR than those without epirubicin, and prolonged mPFS. So our study suggest that epirubicin based combination regimens may be associated with superior efficacy to that without epirubicin, although this should be confirmed by prospective randomly designed research.

In terms of toxic effects, although grade 3-4 leukopenia and gastrointestinal toxicities of epirobicin based regimen group occurred in more than 40% of patients, the differences of none hematologic and hematologic toxicities were not statistically significant between two groups, and the usage of epirubicin had not caused cardiac toxicity with statistical significance. Also, no major side effects or severe complications that could be attributed to epirubicin based chemotherapy administration were reported. This suggests that the epirubicin based regimens were well tolerated and the addition to fist line chemotherapy for advanced STS was feasible.

On our multivariate analysis, anthracyclines based chemotherapy and ECOG performance status 0-1 were identified as favorable factors for progression. Performance status is a well-known prognostic factor of metastatic soft tissue sarcoma in general (Van Glabbeke et al., 1999; Maurel et al., 2009; Kroep et al., 2011). In other literature (Van Glabbeke et al., 1999; Penel et al., 2012), further favorable prognostic factor for survival were the absence of bone or multiple organ metastases, young age, and high histopathologic grade, synovial or liposarcoma histology, radiotherapy, radical metastasectomy, et al. The sample size of our cohort was not large enough to detect more predictive factors. This is why our cohort is not accordance with published studies.

We conclude that palliative chemotherapy in advanced STS should be regarded as a standard treatment option in the management of advanced STS with approximately half of patients deriving clinical benefit. The results of this study indicate that epirubicin based regimens could be associated with better efficacy than regimens without epirubicin at first-line setting for patients with advanced STS, and were safe and well-tolerated regimens, although this has yet to be confirmed in prospective randomized trials.

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