RESEARCH COMMUNICATION

# Efficacy and Toxicity of Gemcitabine Plus Docetaxel Combination as a Second Line Therapy for Patients with Advanced Stage Soft Tissue Sarcoma

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## Abstract

**Purpose: To assess the safety and efficacy of a gemcitabine plus docetaxel regimen as a second line therapy for patients with advanced soft tissue sarcoma (STS) resistant to doxorubicin and ifosfamide-based therapy. Patients and Methods: Medical records of 64 patients with advanced STS who received gemcitabine plus docetaxel regimen as a second line treatment between May 2006 and June 2011 were examined. All patients had been previously treated with doxorubicin plus ifosfamide-based regimen at first line setting. Patients received gemcitabine 900 mg/m$^2$ on days one and eight intravenously over 90 minutes, followed by docetaxel 75 mg/m$^2$ on day eight intravenously over one hour. Cycles were repeated every 3 weeks. Results: The male-to-female ratio was 37/27 and the median age was 44 years (range; 19-67 years). Objective responses were observed in 13 (20.3 %) patients (2 CR, 11 PR) and stable disease in 21 (32.8 %). Total clinical benefit (CR+PR+SD) was observed in 34 (53.1 %). Median overall survival (OS) was 18 months (95% confidence interval (CI):12.1-23.9) and Median time to progression (TTP) was 4.8 months (95% CI: 3.6-6). A total of 243 cycles of chemotherapy were administered. The median number of cycle was 3 (range;1-11). The most common grade 3-4 hematologic toxicity was neutropenia (35.9 %). The most common nonhematologic toxicities consisted of nausea/vomiting (37.5 %), mucositis (32.8 %), peripheral neuropathy (29.7%), and fatigue (26 %). There was no toxicity-related death. Conclusion: The combination of gemcitabine plus docetaxel is an active and tolerable regimen as a second line therapy for patients with advanced soft tissue sarcoma who have failed doxorubicin and ifosfamide-based therapy.**

**Keywords:** Gemcitabine - docetaxel - advanced soft tissue sarcoma - second line therapy - Turkey

*Asian Pacific J Cancer Prev,* **13**, 463-467

## Introduction

Soft tissue sarcomas (STSs) are relatively rare and heterogeneous malignancies originating from mesenchymal cell with distinct clinical and pathological features. STSs account for less than 1% of all new cancer cases each year, but have an aggressive biologic behavior and poor prognosis (Jemal et al., 2006). Advanced and metastatic STSs are currently treated by doxorubicin and/or ifosfamide-based regimens at first line setting. As a first line therapy, combination therapy of both drugs accounts for an objective response (OR) of 23% to 48% (Schutte et al., 1990; Edmonson et al., 1993; Santoro et al., 1995; Le Cesna et al., 2000; Maurel et al., 2009). Current treatment options are limited for patients with recurrent or advanced soft tissue sarcoma refractory to these 2 drugs.

The combination of gemcitabine plus docetaxel demonstrated in vitro synergism (Leu KM et al., 2004, Maki RG, 2007). In a single-institution study, Hensley et al (2002) reported that the combination of fixed dose rate gemcitabine and docetaxel achieved an objective response rate of 53% in pretreated patients with unresectable leiomyosarcoma. However, prospective confirmation of the activity of gemcitabine plus docetaxel was also reported by Maki et al. (2007) in a randomized phase II trial including different soft tissue sarcomas. In that study, objective response rate and median overall survival were 16% and 17.9 months, respectively.

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Here, we aimed to assess the safety and efficacy of a gemcitabine plus docetaxel regimen as a salvage treatment for patients with advanced soft tissue cancer.

## Materials and Methods

*Patients*

Medical records of 64 patients with advanced stage soft tissue cancer who received gemcitabine plus docetael regimen as a second line treatment between May 2006 and June 2011 were retrospectively examined. All patients had been previously treated with doxorubicin plus ifosfamide-based regimen at first line setting. Patients were required to have histologically proven, unresectable or metastatic soft-tissue sarcoma. Other inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status (PS) 0-2, life expectancy of > 3 months, age between 18 and 75 years, no other active primary malignancy, no concurrent uncontrolled medical illness condition including classes III or IV cardiac dysfunction as defined by the New York Heart Association, adequate bone marrow (WBC> 4000/$mm^3$ and or neutrophil count >1500/$mm^3$, platelets>100000/$mm^3$), adequate liver (total bilirubin < 2mg/dl, aspartate aminotransferase or alanine aminotransferase < 3 times the upper limit) and renal function (blood urea nitrogen < 30 mg/dl, serum creatinine < 1.5 times the upper limit).

Treatment plan

Chemothearpy was administered through a central venous catheter placed in the subclavian vein or directly into a peripheral venous routes. Patients received gemcitabine 900 mg/$m^2$ on days one and eight intravenously over 90 minutes, followed by docetaxel 75 mg/$m^2$ on day eight intravenously over one hour. All patients received 32 mg/day methylprednisolone before the day, on the day and after the day of treatment to prevent docetaxel hypersensitivity for all chemothrapy cycles. In addiation, a 5-hydroxytryptamine type 3 receptor antagonist, dexamethasone and metoclopramide were given as antiemetic prophylaxis before every chemotherapy cycle. Cycles were repeated every 3 weeks. Treatment was continued until the documented disease progression, unacceptable toxic effects or patient's refusal.

Toxicity and dosage modifications

Advers events were evaluated and graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. In the event of grade 3 or 4 hematologic toxicity, the doses of both drugs were reduced by 25 % for subsequent cycles. Chemotherapy cycles were delayed if the patient's absolute granulocyte count was < 1500/mm3 or platelet count was < 100000/mm3 on the day of infusion. In cases of grade 3 or 4 nonhematologic toxicity other than alopecia (neurotoxicity, liver toxicity,e.g), the doses of both docetaxel and gemcitabine were reduced 25-35 % in the next cycles.

Evaluation of response

Physical examination, complete blood counts, chemistry were performed after each cycle. Response to treatment was assessed following every 2 consecutive cycles by computed tomography of the abdomen and/or the thorax. Response was evaluated using RECIST criteria. Responders were defined as complete response (CR, disappearance of all measurable and nonmeasurable lesions) or partial response (PR, >30 % reduction of the two lesions with the largest diameter). Progressive disease (PD) was defined as an increase of more than 25 % in tumour size. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Statistical Analysis

Time to progression (TTP) was calculated from the first day of treatment until progression or the last day of follow up without disease progression. The proportion of responses and 95% convidence intervals (95% CIs) were determined. The overall survival (OS) time was measured as the period from the start of chemotherapy until death from any cause or until the date of the last follow up. OS and TTP were assessed by Kaplan-Meier methodology. SPSS version 12.0 statistical software ( SPSS, Chicago, IL) was used for all statistical analyses.

**Table 1. Patient Characteristics**

| Characteristics | No. (n=64) |
|---|---|
| Median age, yr (range) | 44 (19-67) |
| Male/female | 37/27 |
| ECOG performance status | |
| 0-1/2 | 17/47 |
| Initial localization | |
| Extremity/trunk | 34 |
| Retroperitoneal/abdominal | 26 |
| Other | 2 |
| Histology | |
| Leiomyosarcoma | 14 |
| Nonleiomyosarcoma | 50 |
| Undifferenciated sarcoma (NOS) | 30 |
| Liposarcoma | 3 |
| Angiosarcoma | 3 |
| Fibrosarcoma | 6 |
| Synovial sarcoma | 4 |
| MFH | 2 |
| Others | 2 |
| Grade | |
| Grade I | 5 |
| Grade II | 18 |
| Grade III | 41 |
| Prior chemotherapy | |
| IMA | 64 |
| Number of involved organs | |
| 1 | 40 |
| 2 | 18 |
| ≥ 3 | 6 |
| Sites of metastases | |
| Lung | 38 |
| Liver | 29 |
| Bone | 14 |
| Primary origin | 5 |

* 'NOS: not otherwise specified, MFH: malignant fibrous histiocytoma, IMA:Ifosfamide, mesna, doxorubicin

## Results

*Patients Characteristics*

The basal characteristics of the patients are shown in Table 1. The male-to-female ratio was 37/27 and the median age was 44 years (range; 19-67 years). Seventeen

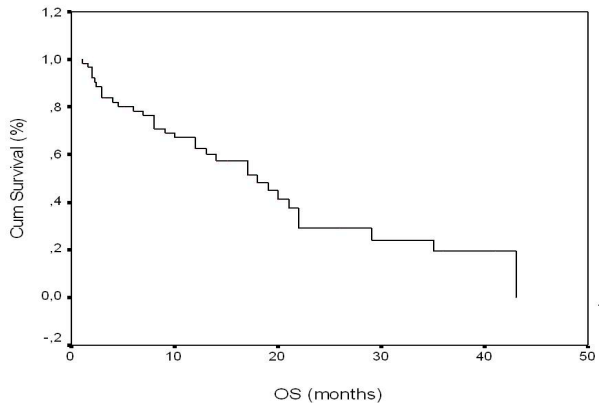


**Figure 1. Median Overall Survival (OS) was 18 Months (95% CI: 12.1-23.9).**

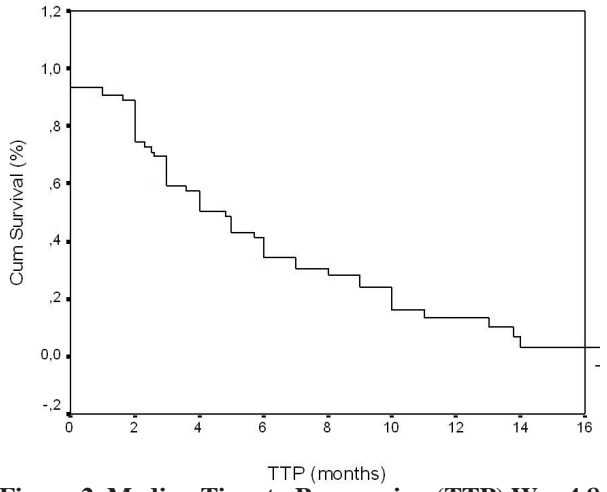


**Figure 2. Median Time to Progression (TTP) Was 4.8 Months (95% CI:3.6-6).**

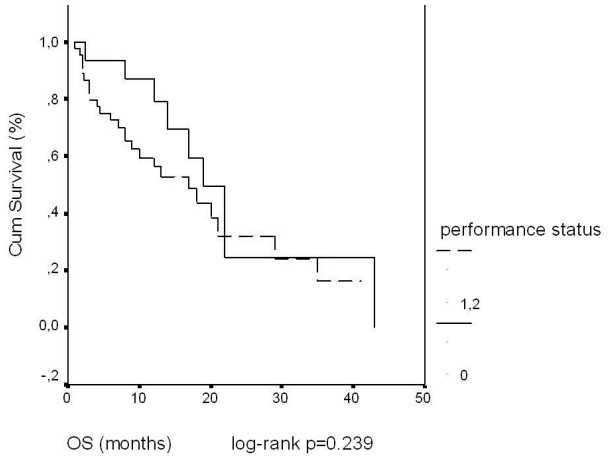


**Figure 3. The Difference between ECOG PS-0 and ECOG PS- 1/2 Survival was not Statistically Significant**

patients (26.6 %) had an Eastern Cooperative Oncology Group performance status of 0. Forty-seven (73.4%) patients had an ECOG of 1-2. All patients had metastatic disease at the beginning of treatment. All patients had received doxorubicin and ifosfamide-based chemothrapy regimen as a first line therapy. The major involved organs were lung, liver, bone and primary region.

*Efficacy and survival*

The median follow-up duration of all patients was 21 months (range; 3-29 months). Complete response and partial response were observed in 2 (3.1 %) patients and in 11 (17.2 %) patients, respectively. Two patients who achieved clinical complete response were ECOG PS-0. Stable disease and disease progression were observed in 21 (32.8 %) and 30 (46.9 %) patients, respectively. Total clinical benefit (CR+PR+SD) was observed in 34 (53.1 %) patients. Median overall survival (OS) was 18 months (95% confidence interval (CI):12.1-23.9) (Figure 1). For all patients, 1 and 2-year survival rates were 62.6% and 28.9%, respectively. Median time to progression (TTP) was 4.8 months (95% CI: 3.6-6) (Figure 2). The patients with ECOG PS-0 had slightly a longer overal survival than patients with ECOG PS- 1/2, but it was not statistically significant [19 months (95%CI:14.7-23.3) vs 17 months (95%CI: 9.1-24.9), log-rank p= 0.239] (Figure 3).

**Table 2. Toxicity (n=64)**

| Toxicity | No. of patients (%) | |
|---|---|---|
| | All grades | Grade 3/4 |
| Hematologic toxicity | | |
| Neutropenia | 37 (57.8%) | 14 (21.9%) |
| Anemia | 16 (26 %) | 3 (4.7% ) |
| Thrombocytopenia | 13 (20.3 %) | 0 |
| Non-hematologic toxicity | | |
| Nausea/vomiting | 24 (37.5%) | 2 (3.1 %) |
| Mucositis | 21 (32.8%) | 0 |
| Peripheral neuropathy | 19 (29.7%) | 4 (6.3%) |
| Fatigue | 16(26 %) | 0 |
| Diarrhea | 11 (17.2%) | 0 |
| Hepatotoxicity | 10 (15.6%) | 0 |

*Toxicity*

A total of 243 cycles of chemotherapy were administered. The median number of cycles was 3 (range, 1-11). Adverse events are shown in Table 2. Grade 1/2 neutropenia and grade 3/4 neutropenia was observed in 23 (35.9 %) and 14 (21.9 %) patients, respectively. Grade 1/2 thrombocytopenia was observed in 13 (20.3%) patients. Grade 1/2 anemia was observed in 13 (20.3 %) patients. The most common nonhematologic toxicities consisted of nausea/vomiting (37.5 %), mucositis (32.8 %), peripheral neuropathy (29.7%), fatigue (26 %), diarrhea (17.2%), and hepatotoxicity (15.6%). Dose reductions of 25-35 % were performed in 14 (21.9 %) patients due to grade 3/4 neutropenia. There was no toxicity-related death.

## Discussion

The combination of gemcitabine plus docetaxel may have an important role for patients with advanced or metastatic soft tissue sarcoma (STS) who have failed to doxorubicin and ifosfamide-based regimens. In our study, this regimen has shown a total clinical benefit rate of 53.1 % (n=34), a median OS of 18 months and a median TTP of 4.8 months in patients with advanced soft tissue sarcoma including different histological subtypes. The high rates of both OS and TTP were particularly interesting and these results could be decisive for second line treatment of patients with pretreated soft tissue sarcomas.

Gemcitabine is a fluorinated analogue of the nucleoside deoxycytidine. The parent form is converted active di- and

triphosphate metabolites after successive intracellular phosphorylation (Heinemann et al., 1988). While the diphosphate form inhibits ribonucleotide reductase, the triphosphate form is incorporated into DNA and blocks DNA synthesis (Iwasaki et al., 1997). Single agent gemcitabine exhibited limited activity yielding 6 % ORR and 47% SD for patients with pretreated adult type STS (Hartmann et al., 2006). Docetaxel is an agent that stabilizes tubulin and inhibits mitotoc and interphase cellular functions (Schiff et al., 1979; Rowinsky et al., 1992). Single agent docetaxel achieved 0 % to 17 % ORR in second line therapy for patients with pretreated adult type STS (Van Hoesel et al., 1994; Verweij et al., 2000). Thus, single agent docetaxel also appear to have limited activity.

Leu et al. (2004) demonstrated that sequential treatment with gemcitabine followed by docetaxel has created synergistic activity on SAOS-2 sarcoma cells and MCF-7 breast cancer cells. In that study, overall response rate and median OS was seen as 43% and 13 months, respectively. Because of gemcitabine plus docetaxel combination have a synergistic effect, this regimen appears promising in patients with STS who have failed doxorubicin and ifosfamide-based therapy. In a phase II study, Hensley et al. (2002) reported that fixed-dose rate gemcitabine plus docetaxel is tolerable and highly active in treated and untreated patients with leiomyosarcoma. In that study, gemcitabine was given on day 1 of successive cycles of therapy over 30 or 90 minutes, a day on which docetaxel was not used. The time above a threshold of 10 $\mu$M was greater with the 90 minutes infusion time of gemcitabine (1.3 versus 0.88 hours;p=0.0008). In addition, the objective response rate and median overall survival were also reported as 53 % and 17.9 months, respectively. In a another phase II study reported by Hensley et al. (2008) the fixed-dose rate gemcitabine plus docetaxel was evaluated only as a second line therapy in patients with metastatic uterine leiomyosarcoma. In that study, the objective response rate and median OS were demonstrated as 27% (6.3% CR) and 14.7 months, respectively. In addition, the side effect profile for fixed-dose rate gemcitabin plus docetaxel was found acceptable.

The side effect results of the above-mentioned three studies were similar to our study. In our study, the most common hematologic and non-hematologic toxicities were neutropenia (57.8%) and nausea/vomiting (37.5%), respectively. Pulmoner toxicity was not observed. Dose reductions of 25-35 % were performed in 14 (21.9 %) patients due to grade 3/4 toxicity. There was no toxicity-related death. When compared with the above-mentioned two studies, the objective response rate of our study was found slightly lower because of our study involves various histological subgroups (20.3% vs 27% vs 53%).

In a retrospective trial reported by the Groupe Sarcoma Français, gemcitabine plus docetaxel combination was evaluated for patients with STS whose resistant to cytotoxic agents such as doxorubicin and ifosfamide. The histological sub-groups of the patients included in the study were similar to our study. In that study, objective response rate and median OS was reported as 18.4% and 12.1 months, respectively (Bay et al., 2006). The objective response rate of that study is similar to our study (18.4 vs 20.3), whereas, the median survival time was longer in our study (12.1 months vs 18 months). In addition to the above-mentioned data, prospective confirmation of the activity of gemcitabine plus docetaxel had been also demonstrated in a randomized phase II trial including different soft tissue sarcomas. In that study, both objective response rate and median overall survival were reported similar to the results of our study (16% vs 20.3% and 17.9 months vs 18 months) (Maki et al., 2007). Grade 3-4 pulmonary toxicity observed in same study was not observed in our study.

In conclusion, the combination of gemcitabine plus docetaxel is a highly active regimen in second line therapy for patients with advanced STS who have failed doxorubicin and ifosfamide-based therapy. This regimen should be considered as a treatment option for second line therapy in patients with advanced STS.

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