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Treatment of Soft-Tissue Sarcoma: Results from the Drug Shortage Era

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Introduction: Soft tissue sarcoma is a disease of mesodermal tissues of extremities, trunk, head and neck. The backbone of treatment in both locally advanced and metastatic disease depends mainly on both Ifosfamide and Anthracyclins. Shortages in one of the former drugs can decrease the possibility of response and complicate the surgical decision.

Purpose of study: To evaluate the impact of Anthracyclin shortage on both response rate and progression free survival in patients with locally advanced and metastatic soft tissue sarcoma.

Patients and methods: The study was performed at Al Bairouni university cancer center in Damascus, Syria. 236 patients with both locally advanced an metastatic soft tissue sarcoma were included in the study treated with (Ifosfamide 3 gr/m^2 for 3 days + CDDP 35 mg/m^2 for 3 days) with G-csf support. 3 cycles were given (21 days apart). Doxoruicin was replaced with Cisplatin due to Anthracyclin shortage in 2012.

Results: CT-Scan and/or MRI performed 14 days after the 3rd cycle which showed a complete response in 62 out of 87 patients presented with metastatic disease (71%) with a P value of 0.07. In the other hand, treatment showed partial response in 34 out of 149 patients presented with locally advanced disease (22%) with a P value of 0.87. best responders were patients with MFH, Liposarcoma, Rhabdosarcoma and Synovilal sarcoma. Side effects and toxicities were acceptable and manageable.

Conclusion: The new combination gave a good response rates in both locally advanced and metastatic settings, however, the combination showed a short lasting response rates in metastatic disease showing a negative impact on treatment of soft tissue sarcoma patients, the thing that makes drug shortage a major challenge for oncologists worldwide.

Introduction

Soft tissue sarcomas are malignant tumors that arise in any of the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). The reported international incidence rates range from 1.8 to 5 per 100,000 per year [1] with 11410 newly diagnosed cases in the United States in 2013 and 4390 deaths [2]. The risk of sporadic soft tissue sarcomas is increased by prior radiation therapy and, in the case of lymphangiosarcoma, by chronic lymphedema. The chemicals Thorotrast, vinyl chloride, and arsenic are also established carcinogens for hepatic angiosarcomas [3-5].

Soft tissue sarcomas occur with greater frequency in patients with Nevoid basal cell carcinoma syndrome (Gorlin syndrome: PTC gene mutation), Gardner syndrome (APC mutation), Li-Fraumeni syndrome (p53 mutation), Tuberous sclerosis (Bourneville disease: TSC1 or TSC2 mutation), von Recklinghausen disease (neurofibromatosis type 1: NF1 mutation) and Werner syndrome (adult progeria: WRN mutation) [3-5].

Since the selection of treatment is determined by the grade of the tumor, it is essential to have a careful review of the biopsy tissue by a pathologist who is experienced in diagnosing sarcomas. Complete staging and treatment planning by a multidisciplinary team of cancer specialists is required to determine the optimal treatment for patients with this disease. There is evidence that at least some favorable clinical outcomes may be associated with referral to a specialized sarcoma treatment center.

In a population-based consecutive series of 375 soft tissue sarcoma patients in Sweden, local recurrence rates of resected tumors were higher in patients who were not referred to the specialized center: in 35 of 78 (45%) patients not referred; in 24 of 102 (24%) patients referred after initial surgery or incisional biopsy; and in 36 of 195 (18%) patients referred prior to any surgical procedure (P = .0001 for the difference between those never referred vs. those referred prior to any surgical procedure) [6]. The prognosis for patients with adult soft tissue sarcomas depends on several factors, including: patient's age, size, histologic grade, mitotic activity and stage [7]. Factors associated with a poorer prognosis include the following: age older than 60 years, Tumors larger than 5 cm in greatest dimension and High-grade histology with high mitotic activity [8]. Although low-grade tumors are usually curable by surgery alone, higher-grade sarcomas (as determined by the mitotic index and by the presence of hemorrhage and necrosis) are associated with higher local-treatment failure rates and increased metastatic potential. Immunohistochemistry and cytogenetic studies determine the histologic subtypes, for example: S100 antigen suggests neural sheath origin, Cytokeratin suggests Epithelioid or synovial cell origin, and factor VIII-related antigen suggests endothelial origin. Likewise, some subtypes of sarcomas have characteristic genetic markers, but these markers are not generally used in the routine clinical setting (e.g., t(X;18)(p11;q11) in synovial sarcomas and t(12;16)(q13;p11) in myxoid and round-cell sarcomas) [9-11]. Lymph node involvement in soft tissue sarcomas of adulthood is rare but is somewhat more frequent in some subtypes (e.g., rhabdomyosarcoma, vascular sarcomas, clear cell sarcomas, and epithelioid sarcomas) when they are high grade [12]. The role of adjuvant chemotherapy is not completely clear. The investigation of its use falls into two categories or generations pre- and post-Ifosfamide regimens. Subsequent chemotherapy trials were performed using Anthracycline and Ifosfamide combinations in patients who primarily had extremity or truncal soft tissue sarcomas. The data are conflicting, and the issue is still not settled. In a small feasibility study, 59 patients with high-risk soft tissue sarcomas, 58 of whom had an extremity or trunk as the primary site, underwent primary resection plus PORT and were randomly assigned to observation versus a dose-dense regimen of six 14-day courses of Ifosfamide, Dacarbazine (DTIC), and doxorubicin (IFADIC regimen) with granulocyte colony-stimulating factor (G-CSF) bone marrow support and Mesna uroprotection [13]. There were no statistically significant differences in OS or relapse-free survival (RFS), but the study was severely underpowered. In a second trial performed by the Italian National Council for Research, high-risk patients were treated with local therapy (i.e., wide resection plus preRX or PORT, or amputation as clinically necessary) and were then randomly assigned to observation versus five 21-day cycles of 4-epidoxorubicin (Epirubicin) plus Ifosfamide (with Mesna and G-CSF) [14,15].

In summary, the impact of adjuvant chemotherapy on survival is not clear but is likely to be small in absolute magnitude. Doxorubicin is a mainstay of systemic therapy in the management of locally advanced and metastatic soft tissue sarcoma. Other drugs that are thought to have clinical activity as single agents are Ifosfamide, Epirubicin, Gemcitabine, and Paclitaxel [16-18]. A subsequent meta-analysis of all three published randomized trials of chemotherapy regimens that contained Ifosfamide versus those that did not came to similar conclusions: tumor response rates were better when the regimen included Ifosfamide (RR_{resp} = 1.52; 95% CI, 1.11–2.08), but mortality at 1 year was not ($RR_{mortality}$ = 0.98; 95% CI, 0.85–1.13) [19].

Many countries are experiencing a rapidly increasing frequency of drug shortages, which have caused numerous difficulties for clinicians, health care facilities, patients, and federal regulators [20]. Drug shortages are caused by many factors, including difficulties in acquiring raw materials, manufacturing problems, regulatory issues, and business decisions, as well as many other disturbances within the supply chain and sanctions as well [21].

Patients and Methods:

Patients

The study was carried out at Al Bairouni university hospital which is the leading cancer center in Syria with more than 11000 newly diagnosed cancer cases per year. All biopsies were reviewed by a referenced pathologist and the final diagnosis was provided in compliance with the published world health organization (WHO) as illustrated in Table 2. Age of studied patient was between 17 and 62 years with a median of (38 years). Patients with both locally advanced and metastatic disease with a good performance status (0,1 and 2) were included. 236 patients were included after signing an informed consent and they were divided into two groups: metastatic (87 patients) and locally advanced (149 patients).

Treatment plan

In the light of Doxorubicin shortage in 2012 (in our hospital), a new plan was made employing Cisplatin instead of Doxorubicin. So patients were treated with (Ifosfamide 3 gr/m^2 for 3 days + CDDP 35 mg/m^2 for 3 days) with G-csf support, (this plan was developed in compliance with the ethical and medical committee of the Syrian association of medical oncology and ministry of health). 3 cycles were given (21 days apart) before a new radiologic evaluation was made to assess response. Responders in metastatic setting continued on the same protocol till progression, while responders in locally advanced disease were referred to surgery. Response was assessed according to RECIST criteria (Response Evaluation Criteria in Solid Tumors) as illustrated in Table 1.

Table 1: Response according to RECIST criteria

Complete Response (CR)	Disappearance of all target lesions for a period of at least one month
Complete Response Unknown (CRU)	Complete response with persistent imaging abnormalities of unknown significance
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameter of measures lesions (target lesions), taking as reference the baseline sum of the longest diameter.
Stable Disease (NR/SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started
Progressive Disease (PD)	A 20% or greater increase in the sum of the longest diameter of measured lesions (target lesions), taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Baseline and treatment assessment

Patients underwent a medical history, physical examination, and tumor measurement of palpable lesions, as well as lesions assessed by imaging techniques (computed tomography and MRI). Treatment responses: complete response (CR), unconfirmed CR (uCR), partial response (PR), stable disease and progressive disease were classified according to the Recist criteria.

Table: 2 Characteristics of patients at the baseline

Median age	38 (17-62) years
Sex (male/female)	(145/91)
Locally advanced	149
Metastatic disease	87
PS 0,1	186
Metastatic sites Lung Abdomen Liver	 53 (60%) 7 (8%) 27 (32)

The most frequent pathologic subtypes are: malignant fibro histocytoma, liposarcoma, rhabdomyosarcoma and synovial sarcoma as illustrated in Table 2.

Table: 2 Pathologic subtypes

Pathologic subtypes	number	percentage
MFH	83	35%
liposarcoma	44	18%
rhabdosarcoma	38	16%
Synovial sarcoma	31	13%
chondrosarcoma	20	8%
fibrosarcoma	10	4%
Non-uterine leiomyosarcoma	10	4%

Statistical analysis

Time-to-event analyses were conducted for progression-free survival (PFS) using the Kaplan–Meier method, from the date first favorable response was attained, and stratified by line of therapy where favorable response was first observed. The date of favorable response was the date when three cycles of chemotherapy were completed.

Results

This study was carried out on 236 patients diagnosed with soft tissue sarcoma with different subtypes, 87 out of 236 (36%) presented with metastatic disease. 91 patients were female (38%). MFH was the most frequent histologic subtype (35%). Treatment commenced with (Ifosfamide 3 gr/m² for 3 days + CDDP 35 mg/m² for 3 days) with G-csf support for three cycles repeated every 21 days. The first evaluation was CT-Scan and/or MRI performed 14 days after the 3rd cycle which showed a complete response in 62 out of 87 patients presented with metastatic disease (71%) with a P value of 0.07. In the other hand, treatment showed partial response in 34 out of 149 patients presented with locally advanced disease (22%) with a P value of 0.87. 31 patients underwent surgical resection while the remaining 3 patients refused to be operated.
Only 16 patients out of 83 (19%) presented with MFH showed response while patients presented with liposarcoma, rhabdosarcoma, synovial sarcoma and chondrosarcoma showed a response of 63%,57%,58% and 40% respectively as illustrated in Table 3.

Table 3: response by histologic subtype

Pathologic subtypes	number	Responders per subtype	percentage
MFH	83	16	19%
liposarcoma	44	28	63%
rhabdosarcoma	38	22	57%
Synovial sarcoma	31	18	58%
chondrosarcoma	20	8	40%
fibrosarcoma	10	1	10%
Non-uterine leiomyosarcoma	10	3	30%

Results from the study also shed light on the progression free survival rate (PFS). The median PFS from the first favorable response in metastatic setting was 6.2 months [95% confidence interval (CI) 5.9–6.8] as illustrated in figure 1.

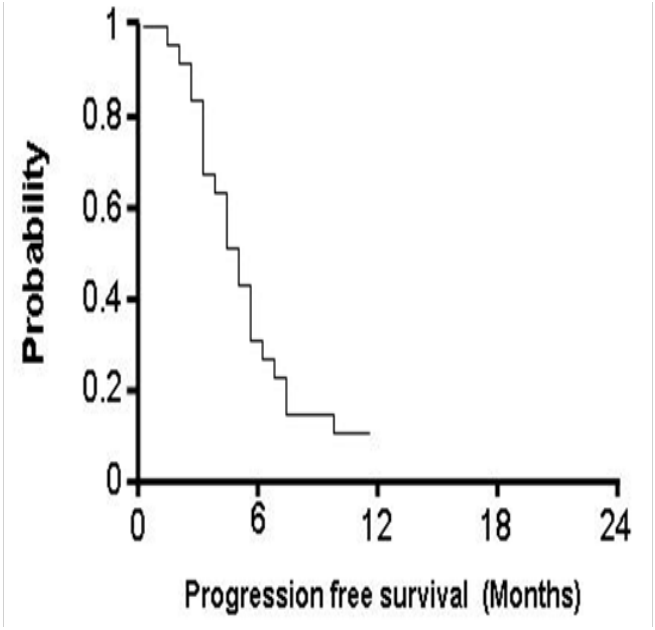

Figure 1: the progression free survival curve in favorable responders

Regarding treatment side effects and toxicities, all patients had alopecia. Vomiting was reposted in 224 patients (94%) while grade II stomatitis was reported in 214 patients (90%). Despite G-csf support, febrile neutropenia was reported in 25 patients (10%), 21 patients of which hospitalized for a median of 4 days. Grade II hemorrhagic cystitis was reported in 28 patients (12%) which was controlled by good hydration and prevented later on by increasing MESNA dose by 25%. All patients complained from anemia of different grades for which 212 patients needed blood transfusion while only 39 patients (13%) complained from grade I thrombocytopenia. The most frequent toxicities are reported in Table 4.

Table 4: side effects and toxicities

Event	Overall	Grade
alopecia	236/236 (100%)	IV
vomiting	224/236 (94%)	II-III
stomatitis	214/236 (90%)	II
Febrile neutropenia	25/236 (10%)	III-IV
Hemorrhagic cystitis	28/236 (25%)	II
anemia	236/236 (100%)	II-III
thrombocytopenia	39/236 (13%)	I

Discussion

In soft tissue sarcoma, Ifosfamide and Doxorubicin form the back bone of treatment in both locally advanced and metastatic disease [10]; however, best treatment has not been defined so far. Standard chemotherapy is based on Anthracyclines as first line treatment. There is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of overall survival [14]. However, a higher response rate may be expected, in particular in a number of sensitive histological types, according to several, although not all randomized clinical trials. Therefore, multiagent chemotherapy with Anthracyclines plus Ifosfamide may be the treatment of choice, especially when a tumor response is felt to be able to give an advantage and patient performance status is good [23]. In this study, we reported 236 cases of both locally advanced and metastatic soft tissue sarcoma with an innovative protocol combining Ifosfamide 3 gr/m² for 3 days + CDDP 35 mg/m². Doxorubicin was replaced with CDDP due to Doxorubicin shortage. Results showed partial response in 34 patients (22%) presented with advanced disease, consequently, responders were eligible for surgery. In the other hand, though 62 patients (71%) presented with metastatic disease showed response (partial and complete) P value was not significant when compared with studies employed anthracyclines like the Dana Farber group who sought to combine all agents with activity against sarcomas in the MAID regimen, consisting of doxorubicin (60 mg/m2), ifosfamide (7.5 g/m2), and DTIC (900 mg/m2) given over a 3-day continuous infusion [24]. In this trial of patients without any prior therapy, 47% of patients responded, and 10% of patients had a complete response. Some patients were able to be rendered disease free after therapy and/or surgery, with several long-term (2 year) survivors.

Regarding progression free survival, the median PFS from the first favorable response in metastatic setting was 6.2 months [95% confidence interval (CI) 5.9–6.8]. Grade II hemorrhagic cystitis was documented in 25% of cases which could be attributed in a part for using generic Ifosfamide: however, the rest of toxicity profile was acceptable and manageable.

Unfortunately, there are no similar studies with which we can compare our results. It is true that the response was good in metastatic setting, however, the duration of response was short when compared with the combination (Ifosfamide and Anthracyclins).

As a result, drug shortage becomes a real challenge in cancer care in both developed and developing countries. Few articles published worldwide shedding the light on this problem especially when we know that some clinical trials were terminated due to drug shortage [25,26]. Shortages also led to delays in chemotherapy, increased toxicities and errors leading to increased risk of side effects and costs of treatment and hospitalization.

References

1) Wibmer C, Leithner A, Zielonke N, et al. (2010) Increasing incidence rates of soft tissue sarcomas? A population-based epidemiologic study and literature review. Ann Oncol 21 : 1106-1111.

2) American Cancer Society. Cancer Facts and Figures 2013. Atlanta, Ga: American Cancer Society.

3) Singer S, Nielsen T, Antonescu CR (2011) Molecular biology of soft tissue sarcoma. In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn) Philadelphia, Pa: Lippincott Williams & Wilkins.

4) Singer S, Maki RG, O'Sullivan B: Soft tissue sarcoma. (2011) In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn) Philadelphia, Pa: Lippincott Williams & Wilkins.

5) Malawer MM, Helman LJ, O'Sullivan B: Sarcomas of bone. (2011) In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn) Philadelphia, Pa: Lippincott Williams & Wilkins.

6) Gustafson P, Dreinhöfer KE, Rydholm A (1994) Soft tissue sarcoma should be treated at a tumor center. A comparison of quality of surgery in 375 patients. Acta Orthop Scand 65: 47-50.

7) Coindre JM, Terrier P, Guillou L, et al. (2001) Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 91: 1914-1926.

8) Vraa S, Keller J, Nielsen OS, et al. (1998) Prognostic factors in soft tissue sarcomas: the Aarhus experience. Eur J Cancer 34: 1876-1882.

9) Singer S, Nielsen T, Antonescu CR: Molecular biology of soft tissue sarcoma. (2011) In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn). Philadelphia, Pa: Lippincott Williams & Wilkins 1522-1532.

10) Singer S, Maki RG, O'Sullivan B: Soft tissue sarcoma. (2011) In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn) Philadelphia, Pa: Lippincott Williams & Wilkins 1533-1577.

11) Malawer MM, Helman LJ, O'Sullivan B: Sarcomas of bone. (2011) In: DeVita VT Jr, Lawrence TS, Rosenberg SA: Cancer: Principles and Practice of Oncology. (9th edn) Philadelphia, Pa: Lippincott Williams & Wilkins 1578-1609.

12) Mazeron JJ, Suit HD (1987) Lymph nodes as sites of metastases from sarcomas of soft tissue. Cancer 60: 1800-1808.

13) Brodowicz T, Schwameis E, Widder J, et al. (2000) Intensified Adjuvant IFADIC Chemotherapy for Adult Soft Tissue Sarcoma: A Prospective Randomized Feasibility Trial. Sarcoma 4: 151-160.

14) Frustaci S, Gherlinzoni F, De Paoli A, et al. (2001) Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 19: 1238-1247.

15) Frustaci S, De Paoli A, Bidoli E, et al. (2003) Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology 65 (Suppl 2): 80-84.

16) Lorigan P, Verweij J, Papai Z, et al. (2007) Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 25: 3144-3150.

17) Nielsen OS, Dombernowsky P, Mouridsen H, et al. (1998) High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC soft tissue and bone sarcoma group. Br J Cancer 78: 1634-1639.

18) Verma S, Younus J, Stys-Norman D, et al. (2008) Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. Cancer Treat Rev 34: 339-347.

19) Stein R. Shortages of key drugs endanger patients. (2011) The Washington Post.

20) Fox E, Birt A, James K, et al. (2009) ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm 66:1399-1406.

21) American Journal of Roentgenology (2010) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) 195: 281-289.

22) Antman K, Crowely J, Balacerzak SP et al. (1993) An intergroup phase III randomized study of Doxorubicin and dacarbazine with or without Ifosfamide and Mesna in advanced soft tissue and bone sarcoma. J clin oncol11: 1276-1285.

23) Elias A, Ryan L, Sulkes A et al. (1989) Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 7:1208-1216.

24) Stein R (2011) Shortages of key drugs endanger patients. The Washington Post.

25) Fox E, Birt A, James K, et al. (2009) ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health Syst Pharm. 66:1399-1406.