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G.A. SERIKBAYEV[1], *D.A. TULEUOVA*[1], *K.M. ORMANOV*[1], *A.K. KURMANALIYEV*[1], *ZH.U. PYSSANOVA*[1]

[1]Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan

Results of using high-dose ifosfamide in disseminated soft tissue sarcomas in Kazakh Institute of Oncology and Radiology

Soft tissue sarcoma (STS) is one of the most adverse forms of tumors from the point of diagnostic and treatment due to its relatively rare occurrence and diversity of histological types.

Surgery is the main treatment for STS.

After local excision as an independent treatment, the frequency of local recurrence is 38.8 to 81.1% [1-4]. STS removal within its pseudocapsules results in tumor recurrence in about 90% cases; extensive local removal of tumor results in 40% recurrence; radical local tumor excision – in 10-15% recurrence [5-7]. Thus, surgical treatment for STS often results in local recurrence what has caused the search for new methods and treatment regimens for STS [3, 8].

The complex treatment of STS on the limbs has expanded the scope of organ-preserving surgery and significantly reduced the local recurrence rate.

Chemotherapy based on doxorubicin and its analogs is now used to increase the 5-year survival of patients with primary and recurring STS. Adjuvant chemotherapy has increased the 5-year survival of STS patients from 53 to 87% [9, 10]. However, disseminated non-operable STS requires independent chemotherapy.

Purpose of the study *was to evaluate the effectiveness of high-dose ifosfamide chemotherapy in disseminated non-operable STS.*

Results: *The treatment of disseminated non-operable STS with ifosfamide has resulted in a complete response in 9 (29%) cases, partial response – 15 (48.4%), progression – 4 (12.9%), and death – in 3 (9.7%) cases. Out of 31 STS patients, 3 had lung mts regression, 1 – main foci regression, 1 – lung mts stabilization, and in 2 cases death might have been caused by pancytopenia and acute kidney deficiency possibly caused by the collapse of the tumor with chemotherapy.*

Conclusion: *high-dose ifosfamide treatment has significantly expanded the capacity of drug treatment of disseminated non-operable STS, especially rhabdosarcoma, synovial sarcoma, as well as malignant tumors of peripheral nerve shells and undifferentiated pleomorphic STS.*

Keywords: *Soft tissue sarcoma, ifosfamide, doxorubicin.*

Introduction. Soft tissue sarcoma (STS) means a heterogeneous group of diseases which includes more than 50 histological subtypes of tumors. STSs are relatively rare and account for 0.2-2.6% of all human malignancies [11-13].

The incidence rate is 1.7‰ in men and 1.6‰ in women. In 60% of cases, STS affects the limbs, of them, 66% of cases affect lower limbs [14-17]. Various authors report frequent hematogenous metastasis in case of STS (24-52.6%), while lymphogenous metastasis is less frequent (2.9-10%) [9, 18-20].

In 2017, 373 new STS cases (1.3% of all malignant neoplasms) were diagnosed in the Republic of Kazakhstan, of them, men – 52%, women – 48%. STS ranked 20th in cancer incidence and 19th in cancer mortality [18].

STS is mainly treated surgically but chemotherapy (CT) is required in case of disseminated non-operable disease [9]. The median survival of patients with disseminated STS amounts to 11 months but approximately 25% of patients live up to 3 years. It could be attributed to tumor biology and/or the CT ineffectiveness [13].

Neoadjuvant, adjuvant, and therapeutic CT is used since recently to increase the 5-year survival of patients suffering from primary and recurrent STSs with generalized tumor process. Doxorubicin and its analogs are the main CT drugs.

CT is currently used as a part of complex treatment, as well as an independent method of treating patients with STS metastases to other organs.

CT with doxorubicin in dosages from 70 to 80 mg/m2 delivers an objective response of 10 to 15% with most frequent partial responses. Monotherapy with ifosfamide produces similar results as doxorubicin: the response rate ranges from 7 to 41% (average – 25%). Ifosfamide is dose-dependent, with a minimum efficacy threshold at a dosage of more than 6 g/m^2 and a significantly higher efficacy at doses above 10 g/m^2 [11].

Comparative studies of monotherapy with doxorubicin and combination therapy with doxorubicin and ifosfamide have been conducted since 1993. In Europe, monotherapy with doxorubicin is recognized as a standard in both adjuvant therapy and the treatment of disseminated forms. The US lean toward combined tactics; the advantages of both schemes are argued for more than 30 years.

Thus, the latest publication of the European Organization for Research and Treatment of Cancer (EORTC) of 2014 contained the results of a multicenter phase III study aimed to compare the efficacy of doxorubicin at a dose of

75 mg/m^2 and a combination of the same dose of doxorubicin with ifosfamide at a dose of 10 g/m^2. The study included 228 patients with locally advanced and disseminated forms of STS. The toxicity was predictably higher in the combination group; PFS was twice higher in the combination group (7.4 months vs. 4.6 months). The immediate efficacy (60% vs. 31%) and overall survival (14.3 months vs. 12.8 months) were also in favor of the combination, but statistical significance was not achieved [12, 21].

Materials and methods. Center for Bone, Soft Tissue Tumors and Melanomas of the Kazakh Institute of Oncology and Radiology has been administering high-dose chemotherapy (HDCT) with ifosfamide since 2014. For four years, this therapy was given to 31 patients with disseminated STS (excluding patients with extraosseous Ewing sarcomas/PNET) in the following cases: 7 (22.6%) cases of rhabdomyosarcoma, 6 (19.4%) – undifferentiated sarcoma, 5 (16.1%) – each of synovial sarcoma and malignant tumors of the peripheral nerve shells, 3 (9.7%) – lipoblastic lipoma, 2 (6.45%) – pleomorphic and leiomyosarcoma, 1 (3.2%) – fibrosarcoma (Table 1). The gender ratio was 1:1, that is, men – 16, women – 15. The average age of patients was 39.7 years (22-71 years). See Table 2 for the distribution of the patients by tumor localization. On average, all patients received 4 courses of systemic polychemotherapy. Median follow-up was 14.7 months.

Table 1 – Distribution of STS patients by histological types

Histological type	No. of patients		Efficacy (%)	
	Abs.	%	Positive response to treatment	No effect
Rhabdomyosarcoma	7	22.6%	100	-
Undifferentiated sarcoma	6	19.4%	65	35
Synovial sarcoma	5	16.1%	100	-
Malignant tumors of the peripheral nerve shells	5	16.1%	60	40
Undifferentiated lipoblastic lipoma	3	9.7%	70	30
Pleomorphic sarcomas	2	6.45%	70	30
Leiomyosarcoma	2	6.45%	100	-
Fibrosarcoma	1	3.2%	-	100

Table 2 – Distribution of STS patients by tumor localization

Tumor localization	No. of patients	
	Abs.	%
Limbs and body surface	21	67.7%
Retroperitoneal space	3	9.7%
Head and neck	3	9.7%
Small pelvis area	3	9.7%
Thorax and abdominal cavity	1	3.2%

Results and Discussion. According to global data, the efficacy of doxorubicin monotherapy varies from 10 to 15%. In our study, the efficacy of ifosfamide amounted to 77.4% (complete and partial response). HDCT with ifosfamide was more efficient for rhabdomyosarcomas (Figure 1). Three out of 31 STS patient showed regression of metastatic foci in the lungs, 1– regression of the primary focus, 1 – stabilization of metastatic foci in the lungs, and 2 cases resulted in death associated with pancytopenia and acute renal failure, possibly associated with the tumor destruction due to the performed CT (Table 3).

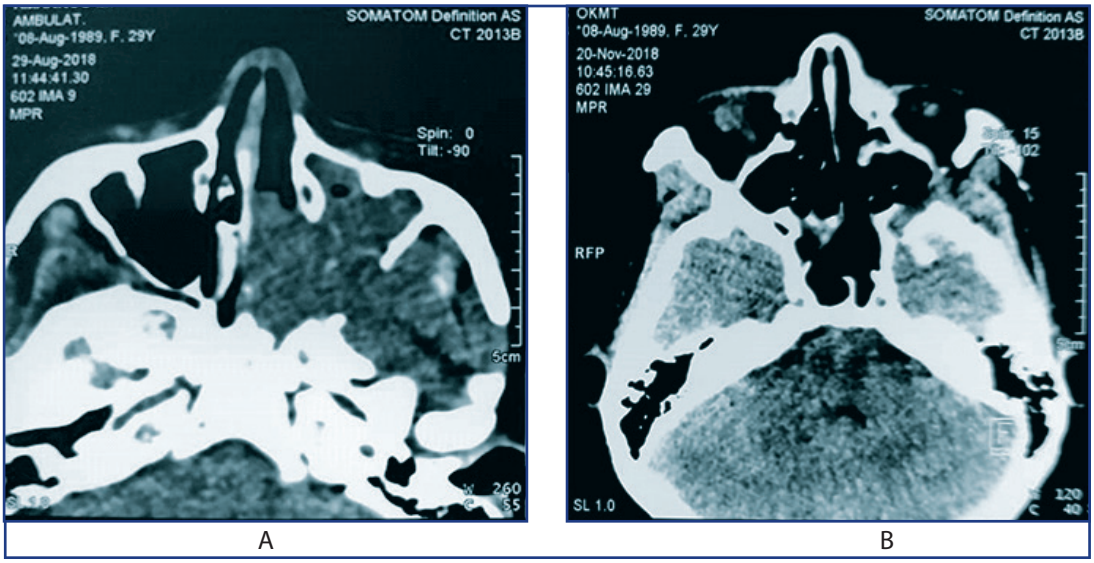

Figure 1 – (A) Rhabdomyosarcoma on the left side of the nasal cavity soft tissues; (B) Complete response after 3 courses of HDCT

Table 3 – HDCT results in STS patients

Effect	Number of patients	
	абс	%
Complete response	9	29%
Partial response	15	48.4%
Progression	4	12.9%
Death	3	9.7%

Conclusion. The introduction of high-dose ifosfamide treatment has significantly expanded the capacity of drug treatment of disseminated STS. Ifosfamide was most effective in treating rhabdomyosarcoma and synovial sarcoma; over 50% of responses were also positive in malignant tumors of the peripheral nerve shells and undifferentiated pleomorphic STS. The obtained positive results – a complete response in 29% of cases and a partial response in 48.4% of cases – have proven the advantage of HDCT with ifosfamide in treating disseminated STS.

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