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TREATMENT OF LARGE OSTEOSARCOMA IN CHILDREN: NEW APPROACH

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***Aim*: To improve the treatment results of patients with locally advanced osteosarcoma with large volume using neoadjuvant chemotherapy (NACT) (ifosfamide at a dose of 18 g/ml) and planning of organ-conserving surgery by evaluating the state of tumor pseudocapsule. *Patients and Methods*: A study group included 46 children aged from 7 to 18 years, mean age — 12 years. In 68% of the patients tumor volume was larger or significantly larger than 200 ml (from 27 to 2400 ml), mean tumor volume was 342 ml. All patients have been examined by X-ray radiography, CT, Doppler ultrasound. Convenient chemotherapy consisted of methotrexate at a dose of 12 g/ml, cisplatin (120 mg/ml) in combination with doxorubicin (75 mg/ml). If such chemotherapy was considered ineffective with the use of an algorithm for determination of chemotherapy efficacy, 2 cycles of chemotherapy with ifosfamide at a dose of 18 g/ml per course have been applied. At the stage of planning of organ-conserving surgery, the state of tumor pseudocapsule was analyzed. In 6 months post-operative chemotherapy was carried out with the use of methotrexate, cisplatin with doxorubicin, ifosfamide at the same doses. *Results*: Myelotoxicity of ifosfamide treatment at a dose of 18 g/ml is comparable to that of to a course of doxorubicin + cisplatin: the depth of leucopenia was significantly higher ($p < 0.05$), the duration of agranulocytosis is similar after such therapies. In the study group, 69.6% patients have reached grade 3–4 pathomorphosis. Organ-conserving surgery was performed in 86.9% of the patients. Local tumor recurrence was registered in 15.2% patients of the study group. 5-year relapse-free survival was achieved in 62 ± 10% ($p = 0.02$), the overall 5-year survival — 76.5 ± 9% ($p = 0.02$). *Conclusions*: Introduction of ifosfamide at a dose of 18 g/ml in the treatment scheme of pediatric patients with locally advanced osteosarcoma along with individualization of pre-operative chemotherapy, pre-operative analysis of NACT efficacy and the state of tumor pseudocapsule during planning stage of organ-conserving surgery significantly improves efficacy of the therapy in patients with large tumor volume.**

***Key Words*: osteosarcoma, children, pseudocapsule tumors, tumor volume, chemotherapy.**

Up to date the treatment efficacy for patients with locally advanced osteosarcoma with large tumor volume (> 200 ml) remains low compared to standard risk patients. For example, according to the data of Bielack et al. [1], 4 year survival of such patients was 42% while in standard risk group 5 year survival yielded 76% [2]. It has been shown that in the cases when tumor volume is larger than 200 ml, microscopic metastatic tumor emboli are already found in lungs and bone marrow [3]. Performance of organ-conserving surgery is contraindicated upon massive muscle injury [4] or significantly advanced soft tissue component (up to 6 cm) or tumor volume larger than 300 ml [4]. Picci et al. [5] have revealed a significant dependence of development of local tumor recurrence on surgical purity of tumor resection margins upon surgical treatment. At the same time Li et al. [6] have shown that the development of local recurrence did not differ between the cases of wide margin resection (> 2 cm) and close margin resection (from 2 to 5 mm from tumor edge). Tumor pseudocapsule is an anatomic structure which separates tumor and healthy tissues [7]. Presently its pre-surgical determination with the use of radiological methods is still problematic. By CT it is possible to determine just an ossification of margin zone "soft tissue-tumor" [8]. With the use of contrast MRT there could be determined a margin between the tumor and soft tissues, but it couldn't be strictly differentiated with peritumoral swelling [9, 10]. Therefore, up to date during planning of operation the surgeons do not consider the state of pseudocapsule [11. 12]. No publications about organ conserving treatment of children with osteosarcoma consider an importance of tumor pseudocapsule identification for surgical planning.

Better results of osteosarcoma treatment directly depend on efficacy of chemotherapy and improve survival indexes [13] and decrease the rates of local tumor recurrence [6].

Rosen et al. [14] have supposed that one of the methods for improvement of osteosarcoma treatment results could be the use of new at the moment preparation ifosfamide at high doses (from 10 to 20 g/ml) and have revealed a direct dependence between preparation dose and efficacy.

In modern literature there is no information on the use of ifosfamide at high dose (18 g/ml) for treatment of children with osteosarcoma. During last 15 years in foreign and native literature there have been published no results about individualization of preoperative chemotherapy

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Abbreviations used: NACT – neoadjuvant chemotherapy; PCT – polychemotherapy.

with the use of radiological methods for evaluation of its efficacy.

The aim of this work was an improvement of treatment efficacy of children with osteosarcoma.

MATERIALS AND METHODS

In the study there have been analyzed clinical records of 46 children from 7 to 18 years old who underwent the treatment in the Department of Pediatric Oncology of Institute of Oncology (presently — National Cancer Institute, Kyiv, Ukraine) in 1999–2006, electronic data base which included USD-images, CT and MRT medical comments, and the results of histological study of medicinal tumor pathomorphism. The protocol № 16 from 30.09.2009 of Committee on Ethics of National Cancer Institute — the work does not violate ethic principles.

Age and gender distribution of children is presented in Table 1. 36 patients (78%) were from 11 to 16 years old. There was equal number of girls and boys.

Table 1. Distribution of children with osteogenic sarcoma by age and gender

	Patient's age, years						Gender	
	7–8	9–10	11–12	13–14	15–16	17–18	Male	Female
Number of patients, n	2	7	11	10	15	1	23	23

Distribution of the patients by tumor localization is shown in Table 2. In he majority of cases malignant tumor was localized in femoral bone (60.8%) or in shin bone (24%).

Table 2. Localization of tumor in children with osteogenic sarcoma

	Localization of tumor in bones					Total
	Femoral bone	Humerus	Fibular bone	Shin bone	Radial bone	
Number of patients, n	28	2	4	11	1	46

Initial tumor volume was determined by CT data. In 28 patients (60.8%) it was larger or significantly larger than 200 ml. Mean tumor volume was 342 ml.

In 1999 we have developed a treatment protocol for pediatric osteosarcoma patients "UNDIOR-99". It included the use of preoperative chemotherapy (neoadjuvant chemotherapy — NACT), analysis of efficacy of administered preparations, and post-operative chemotherapy dependent on an acquired medicinal tumor pathomorphism. The scheme of chemotherapy is presented on Fig. 1 and 2.

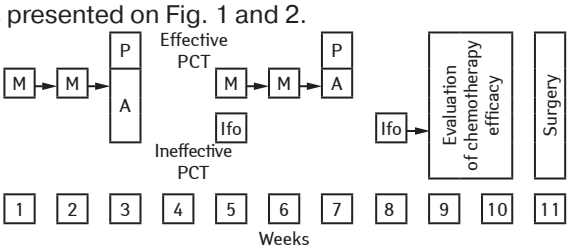

Fig. 1. "UNDIOR-99" Preoperative chemotherapy. *Notes*: M — methotrexate, 12 g/m²; A — doxuribicin, 75 mg/m²; P — cisplatin, 120 mg/m²; Ifo — ifosfamide, 18 g/m².

As it is shown on Fig. 1, in all patients the therapy begins from double course of high-dose methotrexate with 7 days interval. Fourteen days later chemotherapy is continued with intravenous bolus administration of cisplatin combined with doxorubicin. At 5th week of treatment (in 3 weeks after cisplatin + doxorubicin course) there is performed an analysis of treatment effectiveness by the developed algorithm for PCT efficacy determination.

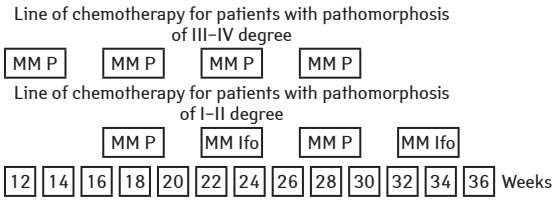

Fig. 2. "UNDIOR-99" Postoperative chemotherapy. *Notes*: M — methotrexate, 12 g/m²; A — doxorubicin, 75 mg/m²; P — cisplatin, 120 mg/m²; Ifo — ifosfamide, 18 g/m².

Upon establishment of efficacy of performed chemotherapy in each individual patient, chemotherapy regimen remains unchanged, and the patient receives the second equal course: double methotrexate, cisplatin with doxorubicin. In the case if performed therapy is considered ineffective, chemotherapy line is switched to double course of high-dose ifosfamide with 3 week interval. Upon tumor pathomorphism of III–IV grades, post-operative chemotherapy has been performed without replacement of chemopreparations, upon tumor pathomorphism of I–II grades — with addition of high-dose ifosfamide (Fig. 2).

Statistical analysis of the data was done with the use of computer program Statistica 6.0 (Statsoft Inc, USA): comparison of independent variables was performed by t-criterion for independent variables, analysis of patient's survival — by Kaplan — Meyer curves.

RESULTS AND DISCUSSION

An efficacy of PCT course was determined by the developed algorithm for determination of NACT efficacy via analysis of patient's tumor state. This algorithm includes a complex of methods: clinical and X-ray methods, the data of CT, MRT, USVD. With the use of USVD the structure and vascularization of tumor soft tissue component were examined. Fig. 3 demonstrates an initial scan of patient's tumor and its scheme prior to chemotherapy. On Fig. 4 one may see the scan of the tumor of the same patient and its scheme after performed preoperative chemotherapy. There has been determined a significant decrease of neomicrovessel numbers in tumor mass and periphery, and formation of tumor pseudocapsule could be observed.

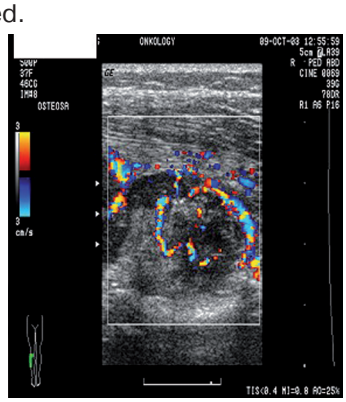

Fig. 3. Scanogram of patient M. prior to chemotherapy. Approximately one hundred microvessels are chaotically placed in tumor mass and periphery, tumor soft tissue component is not separated from muscles.

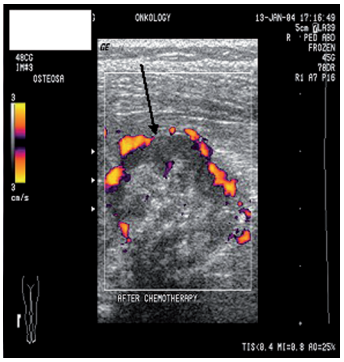

Fig. 4. Scanogram of patient M. after preoperative chemotherapy. Single microvessels in tumor mass and periphery are visualized. Pseudocapsule of tumor could be seen (shown by arrow). Positive effect of NACT

By the data of algorithm for determination of PCT efficacy, effectiveness of chemotherapy course was established only in 7 (15.5%) patients, so further change of chemopreparation was not required. In 1 patient an evaluation of treatment efficacy was not performed because of purulent process in the wound. In other 38 patients negative effect of performed chemotherapy has been registered. After therapy line switch, during pre-operative combined examination, chemotherapy effectiveness was documented in 36 (95%) from 38 patients and PCT efficacy in all 7 patients treated without switch of chemopreparation. In total, by the data of pre-operative combined examination, chemotherapy was effective in 95.5% of the patients. By the data of medicinal pathomorphism, an expressed degree (III–IV by Havos) was registered only in 32 patients (69.6%). The discrepancy in determination of chemotherapy efficacy with the use of combined examination or medicinal pathomorphism is caused by limited accuracy of the developed method (75.5%). Statistical analysis of the data for the cases with switched chemotherapy line with the obtained medicinal pathomorphism, has revealed a significant dependence between these two variables ($p < 0.05$). So, the switch of chemotherapy line significantly affects medicinal pathomorphism.

Myelotoxicity of ifosfamide at the dose of 18 g/ml has been studied. IV grade leucopenia by toxicity scale CTC NCIC was observed in 100% patients treated with high-dose ifosfamide and in 83% patients treated with combination of cisplatin with doxorubicin. In other 17% patients treated with combination of cisplatin + doxorubicin, there has been registered hematologic toxicity of III degree by decreased leukocyte counts.

There has been performed a comparison between maximal leucopenia and duration of agranulocytosis. Maximal leucopenia rates significantly differed after the courses of high-dose ifosfamide and cisplatin + doxorubicin combination. After high-dose ifosfamide course maximal leucopenia was more frequent ($p = 0.0425$) but duration of agranulocytosis in these patients didn't differ significantly from that in children treated with cisplatin + doxorubicin combination ($p = 0.8274$).

In the study of platelet counts after chemotherapy with high-dose ifosfamide or cisplatin + doxorubicin combination it has been shown that IV degree toxicity (platelet counts $< 25 \cdot 10^9$/l) was observed in 16 from 24 (67%) chemotherapy courses with cisplatin + doxorubicin combination and only in 2 from 24 (8%) chemotherapy courses with high-dose ifosfamide. Platelet counts were not decreased after 20 from 24 (84%) chemotherapy courses with high-dose ifosfamide and after 6 from 24 (25%) courses with cisplatin + doxorubicin.

There has been found no significant difference in hemoglobin levels and erythrocyte counts after chemotherapy courses with high-dose ifosfamide or combination of cisplatin with doxorubicin.

So, after high-dose ifosfamide course leucopenia intensity was higher compared to that after the course of cisplatin combined with doxorubicin ($p = 0.0425$), along with this agranulocytosis duration was practically similar in both therapeutic groups ($p = 0.8274$), while the rate of IV degree thrombocytopenia was significantly higher (by 8.3 fold) in the case of cisplatin + doxorubicin combination than in the case of high-dose ifosfamide. These data evidenced on the safety of use of ifosfamide at a dose of 18 g/ml and on possibility of its use in clinical practice.

Pseudocapsuliferous tumors were studied by Doppler USD using an algorithm for determination of chemotherapy efficacy. It has been found that before operation enclosed persistent pseudocapsule was present in 35 patients of the main group. In the cases when pseudocapsule was absent in some tumor region, then with the use of USD there has been performed skin mapping of problematic region with determination of its depth from skin to tumor. Sometimes if pseudocapsule is placed above tumor necrosis zone and is thin-walled, it could be damaged with following efflux of tumor tissue in the wound. Such situation is dangerous because of possible tumor recurrence.

We have performed statistical analysis of the state of pseudocapsule and the risk of development of local tumor recurrence. It has been estimated with significance $p = 0.008$ that closeness of formed tumor pseudocapsule reduces local tumor recurrence after performed radical operative treatment. Therefore, the study of tumor pseudocapsule with the use of USVD prior to the surgery is important for planning of the operative treatment. We suppose that total absence of tumor pseudocapsule should be considered as contraindication for performance of organ-conserving operation, while its partial absence — as relative contraindication for performance of organ-conserving operation which requires preparatory mapping of risk zone and its radical removal.

Also, there has been analyzed the dependence between initial tumor volume and the rate of local recurrence. We have performed a correlation analysis between variables of tumor volume, the rate of recurrence or its absence. No significant correlation between these indexes was revealed ($r = 0.11$).

If tumor volumes were distributed in groups < 100 ml or > 300; 400; 500 ml, their correlation with recurrence cases was also insignificant (r = 0.18; 0.14; 0.12 respectively).

So, these data allow conclude that tumor volume has no influence on the rate of local recurrence. That's why tumor volume could be considered as contraindication for organ-preserving operation only in the cases when it is impossible to cover endoprosthesis or transplant with soft tissues.

Organ-conserving operations were performed in 86.9% patients. Local recurrence was found in 15.2% patients. An index of 5 year relapse-free survival was 62 ± 10% ($p = 0.02$), overall survival —76.5 ± 9% ($p = 0.02$).

In conclusion, introduction of ifosfamide at the dose of 18 g/m^2 in the treatment scheme of pediatric patients with local form of osteosarcoma along with individualization of pre-operative chemotherapy, pre-operative analysis of NACT efficacy and the state of tumor pseudocapsule during planning stage of organ-conserving operations significantly improved oncologic and functional results of the therapy of patients with large tumor volume up to the indexes comparable with standard risk group.

REFERENCES

1. Bielack S, Delling G, Kotz R, ***et al***. Cooperative osteosarcoma study group trial COSS-96 of intensive, risk-stratified chemotherapy for osteosarcoma. Intern Sarcoma Meeting Stuttgart, 2005. 103.

2. Ferrari S, Smeland S, Mercuri M, ***et al***. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. J Clin Oncol 2005; **23**: 8845–52.

3. Bruland ØS, Høifødt H, Sæter G, ***et al.*** Hematogenous micrometastases in osteosarcoma patients. Clin Cancer Res 2005; **11**: 4666–73.

4. Surgery of soft tissue and bone sarcoma. Principles and operative techniques. Shugabeiker PX, Malauer MM, eds. Moscow: Meditsina, 1996: 245–308 (in Russian).

5. Machak GN. Modern possibilities and perspectives of combined therapy of osteogenic sarcoma. Thesis Diss Dr Med Sci, Moskow, 2007 (in Russian).

6. Picci P, Sangiorgi L, Rougraff B, ***et al.*** Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. J Clin Oncol 1994; **12**: 2699–05.

7. Samardziski M, Zafiroski G, Janevska V, ***et al***. Osteosarcoma: diagnosis and treatment. J Pediatr Sci 2010; **2**: 2–15.

8. Rodriguez-Galindo C, Shah N, McCarville B, ***et al.*** Outcome after local recurrence of osteosarcoma. Cancer 2004; **100**: 1928–35.

9. Machak GN, Kochergina NV, Sen'ko OV, ***et al***. Clinico-radiological criteria of risk evaluation at the background of preoperative chemotherapy of osteosarcoma. Union Of Russian Anticancer Organizations. http:netoncology.ru/press/articles/710/712/ (in Russian).

10. Seeger LL, Widoff BE, Bassett LW, ***et al.*** Preoperative evaluation of osteosarcoma: value of gadopentetate dimeglumine-enhanced MR imaging. Am J Roentgeno 1991; **157**: 347–51.

11. Wafa H, Grimer R. Surgical options and outcomes in bone sarcoma. Expert Rev Anticancer Therapy 2006; **6**: 224–29.

12. Grimer R, Athanasou N, Gerrand C, ***et al***. UK guidelines for the management of bone sarcomas. Sarcoma 2010; 2010. Article ID 317462, 1–14.

13. Dahlin DC, Unni KK. Bone tumors. General aspects and data on 8542 cases. Cancer Res 2010; **75**: 567–62.

14. Rosen G, Forscher C. Current combined treatment of high-grade osteosarcomas. Oncology 1995; **9**: http://www.cancernetwork.com/display/article/10165/65653