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TREATMENT OF CHILDREN WITH OSTEOSARCOMA

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ABSTRACT

Osteosarcoma accounts for 3% of all malignant tumors, 35-50% of all malignant bone tumors in pediatric patients. The paper contains statistical data describing the incidence of the child population of osteosarcomas, classification of osteosarcomas, staging principles, a description of the main localizations, as well as a detailed description of the existing treatment protocols for children with osteosarcomas, including personalized therapy.

The literature data are described in detail - the results of treatment of children with osteosarcoma with various courses of chemotherapy, as well as new approaches in treatment, including personalized therapy. But the results of treatment of children with primary metastatic osteosarcoma, relapse and refractory course of the disease remain unsatisfactory.

Molecular biological factors that determine sensitivity to chemotherapy, invasive and metastatic potential of the tumor, as well as the prognosis of the disease, among which special attention is deserved: expression of MGMT protein, methylation of the promoter part of the MGMT gene, expression of ERCC1 proteins, VEGF, CD133, p -STAT3tyr705, C-MYC, expression of RFC1 micro-RNA and the presence of rearrangement of the TOR2A gene. It is important to note the following fact that there was no comprehensive assessment of the value of these markers for the histological response to neoadjuvant chemotherapy and survival rates in patients with osteosarcoma.

Keywords: pediatric oncology, osteosarcoma, chemotherapy, personalized therapy, combination treatment.

Introduction. Osteosarcoma is a primary malignant bone tumor that develops from primitive mesenchymal stem cells capable of differentiating into bone, cartilage or fibrous tissue [20].

Osteosarcoma accounts for 3% of all malignant tumors, 35-50% of all malignant bone tumors in pediatric patients. The frequency of occurrence is 4 cases per 1 million children and adolescents per year. About 60% of cases of osteosarcoma detection are recorded at the age of 10 to 20 years (mainly in the prepubertal and pubertal periods). The gender ratio (boys / girls) is 1.3-1.6: 1 35].

In 50% of cases, the tumor is located in the projection of the knee joint (distal femur, proximal tibial bone). The third place in terms of frequency of occurrence is the lesion of the proximal metadiaphysis of the humerus. The defeat of the axial skeleton (pelvis, spinal column) is detected in 12% of cases [20, 35].

Classification and staging

WHO classification of soft tissue and bone tumors of 2013 (fourth revision) [10].

A localized (locally advanced) variant of osteosarcoma, which occurs in 80% of cases, and a disseminated (primary metastatic) variant, which occurs in 20% of cases, are distinguished.

Histological classification of osteosarcomas:

- low grade, central;
- classic (conventional) version:
- chondroblastic;
- fibroblastic;
- osteoblastic;
- unspecified accuracy;
- telangiectatic;
- small cell;
- high degree of malignancy, superficial.

Staging according to the TNM classification is presented in Table 1.

Treatment. The methods of treatment of osteosarcoma over the past thirty years have not changed. There are five main drugs (cisplatin, adriamycin, methotrexate, ifosfamide, etoposide), which were used in various combinations and doses [1]. The rates of treatment outcome in the world remain approximately the same. In patients with a localized variant of osteosarcoma, 5-year overall survival (OS) does not exceed 75%, 5-year event-free survival (BSV) - 62% (Table 1).

In patients with primary metastatic osteosarcoma, the results are much worse, despite attempts to use high doses of drugs, including high-dose polychemotherapy with transplantation of autologous hematopoietic stem cells. At the same time, the 5-year OM does not exceed 35% on average, the 5-year BSV — 25% (Table 2).

The most significant interest in treating children with a localized osteosarcoma is the study of the Italian and Scandinavian groups (Italian and

Table 1

Staging by TNM

Stage	TNM	Degree of malignancy
IA	T1 N0 M0	low
IB	T2 N0 M0	low
IIA	T1 N0 M0	high
IIB	T2 N0 M0	high
III	T3 N0 M0	any
IVA	Any T N0 M1a	any
IVB	Any T N1 Any MJIюбое Any T Any N M1b	any any

Table 2

The results of the treatment of pediatric patients with localized osteosarcoma

Therapy program	5-year overall survival, %	5-year event-free survival, %
IOR/OS2 the Istituto Ortopedico Rizzoli [2]	75	63
ISG/OS1 (Italian Sarcoma Group) [8]	74	64
ISG/SSG1 (Italian and Scandinavian Sarcoma Group) [9]	77	64
COSS 88/96 (Cooperative Osteosarcoma Study Group) [17]	79	
SSG XIV (Scandinavian Sarcoma Group) [31]		65
NECO93J/95J (Neoadjuvant Chemotherapy for Osteosarcoma) [21]	78	65
BOTG III/IV (Brazilian Osteosarcoma Treatment Group) [28]	61	45
POG8651 (Pediatric Oncology Group) [11]	78	65
SFOP94 (Société Française d'Oncologie Pédiatrique) [22]	76	62
St.Jude CRH OS91 (Children Research Hospital) [18]	74	65
St.Jude CRH OS99 (Children Research Hospital) [5]	79	67
INT0133-COG (+MTP/-MTP) Children's Oncology Group [26]	78/70	67/61
MSKC NY (+PAM) Memorial Sloan-Kettering Cancer Center, NY [25]	94	72
COG INT0133, CCG7943, AOST0121 [25]	47	22
ISG/SSG II (Italian and Scandinavian Sarcoma Group) [26]	55	46
EURAMOS1 [30]	75	59

Scandinavian sarcoma group - ISG / SSGI, SSG XIV), the French Pediatric Oncological Group (Societe Francaise d'Oncologie Pediatricue - SFOP OS94), and EURAMOS1.

Ferrari S. et al. showed the data of the joint study of the Italian and Scandinavian groups (ISG / SSG I), which was conducted from 1997 to 2000. The study included 182 patients. A special feature of neoadjuvant chemotherapy was the use of two courses of monotherapy with high-dose ifosfamide (in a course dose of 15 g / m2) and two courses of MAR (methotrexate (M) 12 g / m2, adriamycin (A) 75 mg / m2, cisplatin (P) 120 mg / m2) in alternating mode. Adjuvant chemotherapy started at week 14. The course dose of adriamycin was increased to 90 mg / m2, the dose of cisplatin to 150 mg / m2, high-dose ifosfamide was administered in PIM chemotherapy courses (cisplatin, ifosfamide, methotrexate) and PAI (cisplatin, adriamycin, ifosfamide).

After removal of the primary tumor focus, a good histological response (therapeutic pathomorphism of grade 3–4) was achieved in 63% of patients, a poor histological response (treatment pathomorphism of grade 1–2) in 37%. At the same time, the 5-year OV and BSV accounted for 77% and 64%. Consequently, the use of high-dose ifosfamide in an alternating mode with the IDA scheme led to an increase in the frequency of achieving a good histological response, but did not affect the rates of OS and BSV [8, 9].

Smeland S. et al. presented the data of the study of the Scandinavian Group (SSG XIV), which was conducted from 2001 to 2005. The study included 63 patients. Neoadjuvant chemotherapy consisted of 2 courses of IDA. High-dose ifosfamide (in a course dose of 10 g / m2) was used in monotherapy in patients with a poor histological response to treatment, only after 5 courses of MAP.

After removal of the primary tumor lesion, a good histological response was achieved in 45% of patients, a poor histological response in 55%. At the same time, the 5-year OV and BSV accounted for 76% and 65%, the 5-year BSV in the group with a good histological response - 89%, with a poor histological response - 48%. Consequently, the use of ifosfamide after MAP courses in the adjuvant mode did not lead to an increase in OS and BSV, and the frequency of achieving a good histological response was lower than in studies in which the MAP scheme was used in an alternating mode with ifosfamide [31].

Le Deley M.C. et al. presented the results of the randomized SFOP OS94 study, which was conducted from 1994 to 2001. The study included 239 patients (120 in group A, 119 in group B).

Neoadjuvant therapy included 7 courses of high-dose methotrexate and 2 courses of monotherapy with adriamycin (in a course dose of 70 mg / m2) in group A or 7 courses of high-dose methotrexate and 2 courses of IE (ifosfamide (I) 12 g / m2, etoposide (E) 300 mg / m2) in group B. In the adjuvant mode, chemotherapy was replaced with IE courses in group A, and AR in group B for patients with a poor histological response, detected after removal of the primary focus. The operative stage of treatment was carried out at 12 and 14 weeks in groups A and B, respectively.

A good histological response was achieved in group A in 43% of patients, in group B in 64%, poor histological response in group A in 57%, in group B in 36% (p = 0.009). The 5-year OM in Group A was 75%, in the Group B - 76%, the 5-year BSV in Group A - 58%, in Group B - 66%. 3-year BSV in group A in patients with a good histological response - 82%, with a poor histological response - 49%, in group B - 77% and 60%, respectively. Consequently, the use of methotrexate, ifosfamide, etoposide in neoadjuvant chemotherapy led to a statistically significant increase in the frequency of achieving a good histological response, but not to an increase in OS and BSV [22]. Of particular interest in the treatment of children with primary metastatic osteosarcoma are the POG IE (Pediatric Oncology group) and ISG / SSG II studies. Goorin A.M. et al. presented the results of a phase II / III non-randomized clinical trial of high-dose ifosfamide and etoposide in patients with primary metastatic osteosarcoma. The study included 43 patients.

Neoadjuvant chemotherapy was represented by 2 courses of IE (ifosfamide (I) 17.5 g / m2, etoposide (E) 500 mg / m2). Removal of the primary tumor lesion was performed after 2 courses of IE at 7-8 weeks of therapy. The timing of the removal of metastatic foci was chosen individually during adjuvant chemotherapy, which included 4 courses of MAP chemotherapy and 3 courses of iE (with a course dose of ifosfamide (i) 12 g / m2) in an alternating mode. A good histological response was achieved in 65% of patients, poor in 35%. However, the 2-year-old RH and BSV were 55% and 45%. Consequently, the use of high-dose ifosfamide in combination with etoposide therapy led to an increase in the frequency of achieving a good histological response, but not indicators of OS and BSV [12].

Boye K. et al. showed the results of the non-randomized study ISG / SSG II, which was conducted from 1996 to 2004. The study included 57 patients with primary metastatic osteosarcoma.

Neoadjuvant chemotherapy included 2 courses of MAPI. Surgical removal of the primary tumor lesion was performed at week 14.

In the adjuvant regimen, 2 courses of ACyVP (adriamycin (A) 90 mg / m2, cyclophosphamide (Cy) 4 g / m2, vepezid (VP) 600 mg / m2) and 2 courses of high-dose chemotherapy VPCarbo (vepezid (VP) 600 mg / m2 , carboplatin (Carbo) 1.5 g / m2) with the support of autologous hematopoietic stem cells. Surgical removal of the primary tumor lesion was performed at week 14.

A good histological response was achieved in 29% of patients, poor in 71%. The 5-year OM and BSV were 31% and 27% [3].

Marina N.M. et al. presented the results of the EURAMOS1 study in patients with a poor histological response after neoadjuvant MAP chemotherapy. Within the protocol, patients are randomly assigned to the MAP treatment lines (methotrexate (M) 12 g / m2, adriamycin (A) 75 mg / m2, cisplatin (P) 120 mg / m2) and MAPIE (ifosfamide (I) 14 g / m2, etoposide 500 mg / m2). In the age group up to 30 years, the MAPIE line of therapy was carried out in 310 patients, the MAPIE line in 308 patients, in the age group up to 20 years - 259 (84%) and 271 (88%) patients. Groups of patients are statistically significantly comparable by gender, age, localization of the primary tumor lesion, the presence of a metastatic lesion, the histological variant of the tumor.

In the group of 541 patients with a localized version of osteosarcoma, 247 events were identified, 118 in patients who received the MAP therapy line, 129 in patients who received the MAPIE therapy line. At the same time, the 3-year BSV was 60% and 57%. In the group of patients with primary metastatic osteosarcoma, 3-year BSV was 24% and 18%, for MAP and MAPIE, respectively. Consequently, this study showed that the use of alternating chemotherapy courses for MAP, IE, and Ai in an adjuvant regimen did not lead to an increase in BSV rates [24].

Treatment outcomes for children with primary metastatic osteosarcoma remain extremely low and the optimal therapeutic strategy is unknown. New programs are being developed around the world taking into account the molecular biological features of

tumor cells that determine sensitivity to chemotherapy (ERCC1 to cisplatin, TOPO2α to anthracyclines and etoposide, MGMT to epigenetic therapy and cisplatin, RFC1 to methotrexate) [4], invasive and metastatic potential of the tumor (stem cell markers - CD133, OCT4; transcription factors - p-STAT3, C-MYC; cytokine-associated signaling pathways - ErbB2, VEGFR1, VEGFR2, PDGFRα, PDGFRβ) [13]. Cui Q. et al. presented the results of a study to determine the expression of MGMT protein (methylguanine - DNA - methyltransferase) and MGMT gene methylation in patients with osteosarcoma in the age group up to 40 years (mean age 17 years) who were treated with cisplatin in single mode, in a course dose of 120 mg / m2. Determination of MGMT protein expression in immunohistochemical (IHC) study was performed in biopsy tumor material in 76 patients, MGMT gene methylation in 51 patients. The result of IHC was considered positive with a high expression level — more than 30% (3+), with an average expression level — 20-30% (2+), with a low expression level — 10-20% (1+). MGMT protein expression was detected in 52 (68%) patients, low expression level in 27 (35%), medium level in 18 (24%), high level in 7 (9%).

A statistically significant relationship was established between the presence of MGMT protein expression and an increase in the frequency of a poor histological response (p = 0.004). The expression level above 20% was detected in 22 out of 43 (51%) patients in the group of patients with 1–2 degrees of therapeutic pathomorphosis and only in 3 out of 33 (9%) patients in the group with 3–4 degrees of therapeutic pathomorphosis. Methylation of the promoter portion of the MGMT gene was observed in 12 of 51 (23.5%) patients, and the lack of expression of MGMT protein in 14 of 51 (27.5%) patients. A statistically significant relationship between the absence of methylation and the presence of MGMT protein expression (p <0.001) was established. In the group of patients with 1–2 degrees of therapeutic pathomorphosis, the absence of MGMT gene methylation was detected in 36 of 38 (94.7%) patients, and with 3–4 degrees of therapeutic pathomorphosis in 3 of 13 (23%) patients (p <0.001).

Consequently, the data obtained indicate the formation of tumor resistance to treatment with an alkylating agent — cisplatin in patients whose biopsy material revealed no methylation of the promoter portion of the MGMT gene and the presence of MGMT protein expression [4]. Pitano-Garcia A. et al. (Spain sarcoma group) conducted a study to determine the expression of RFC1 micro-RNA (reduced folate carrier 1, a transmembrane protein that provides folate and methotrexate transport to the cell) by real-time polymerase chain reaction (PCR) in a tumor substrate in children with osteosarcoma.

The analysis of 34 samples, biopsy tumor material in 14 children, tumor material metastatic foci in 20 children. In 13 of 14 (92.9%) biopsy specimens, in 11 of 20 (68.8%) metastatic specimens, a low level of RFC1 expression was detected.

A poor histological response after neoadjuvant chemotherapy (3 courses of intravenous doxorubicin at a dose of 75 mg / m2, 3 courses of intra-arterial administration of cisplatin at a dose of 105 mg / m2, 4 courses of intravenous methotrexate at a dose of 14 g / m2) was set up in 45% of cases. The biopsy tumor substrate in this group of patients was characterized by a low level of expression of RFC1 micro-RNA in 90% of cases compared to 60% in patients with a good histological response (p = 0.053). The average level of expression was statistically significantly lower in the biopsy material than in metastatic tumor foci (p = 0.024) [29]. Consequently, in this study, there was a tendency to an increase in the frequency of detecting low expression levels of RFC1 micro-RNA in patients with a poor histological response.

Hattinger C.M. et al. (Italian sarcoma group) presented the results of a study whose goal was to determine the prognostic significance of protein expression ERCC1 (excision repair cross-complementation group 1) in biopsy tumor material in patients with localized osteosarcoma who underwent programmed treatment of ISG / OS-oss and ISG / SSG1. A tumor sample was considered positive in the presence of a score of 2-3: score 1 (1-10% of positive nuclei), score 2 (11-50% of positive nuclei), score 3 (more than 50% of positive nuclei). ERCC1-positive tumor (score 2-3) was detected in 30 patients (30%). During the ISG / OS-oss program in groups of patients with ERCC1-negative / score 1 and ERCC1-positive (score 2-3), the 5-year-old RH and BSV tumor variants were 91%, 38% and 57%, 25% (p = 0.001; p = 0.042), with the ISG / SSG1 program - 82%, 64% and 69%, 36% (p = 0.022; p = 0.028), with both therapy programs - 82%, 50% and 62% , 34% (p <0.001; p = 0.006). Consequently, a statistically significant relationship has been established between the ERCC1-positive variant of the tumor and lower rates of 5-year OS and BSV [16].

Nguyen A. et al. (SFOP) presented the results of a study to determine the prognostic significance of TOP2A protein expression (topoisomerase DNA 2 alfa) and the presence of rearrangement of the TOP2A gene in biopsy tumor material in 105 children with osteosarcoma who were treated using the SFOP protocol OS94. Patients with primary metastatic osteosarcoma were 17%. After neoadjuvant chemotherapy, a good histological response was detected in 56 patients (53%), a poor histological response in 49 (47%). Real-time PCR amplification of the TOP2A gene and the TOP2A gene deletion were detected in 21 (21.2%) and 25 (25.3%) patients. In 53 children (53.5%), no rearrangement of the TOP2A gene was detected. A statistically significant relationship was established between the presence of the TOP2A gene rearrangement (amplification and deletion) and the presence of a good histological response after neoadjuvant polychemotherapy (p = 0.004). There was also a tendency to achieve lower rates of 5-year OM and BSV in patients whose tumor cells showed amplification of the TOP2A gene (p = 0.09 and p = 0.06). The expression of the TOR2A protein was determined in 17 patients by immunohistochemistry. Medium (2+) and high (3+) levels of expression were detected in all patients, expression was above 30% in 12 of 17 children (70.5%). There is no statistically significant relationship between the expression of the TOR2A protein above 30% and the presence of amplification or deletion of the TOP2A gene (p> 0.05) due to an insufficient number of observations [27].

Xiao X. et al. Presents the results of a study of a personalized approach to the prescription of chemotherapy depending on the presence or absence of markers of drug resistance in 28 patients with localized osteosarcoma. The average age in the group of patients was 20.1 g. To determine the sensitivity to chemotherapy, the following markers were used: for doxorubicin - expression of TOP2A micro-RNA, mutation of the ABCB1 gene, mutation of the GSTP1 gene; for cisplatin, expression of micro-RNA ERCC1, BRCA1, mutation of the genes XRCC1-exon6 and XRCC1-exon10, for ifosfamide, mutation of CYP2C9 * 3.

At the same time, a high level of sensitivity to ifosfamide was detected in all patients (100%), to cisplatin in 11 out of 28 (39.2%), to doxorubicin in 6 out of 28 (21.4%); medium and high levels of sensitivity to cisplatin in 17 of 28 (60.7%), to doxorubicin in 20 of 28 (71.4%). Chemotherapy, taking into account the

sensitivity of the tumor to drugs, was performed in 8 of 28 patients (28.5%). In this group, only 1 relapse of the disease was detected, while in the rest of the 20 patients 4 relapses of the disease were detected, in 1 case progression during neoadjuvant chemotherapy and in 1 case fatal outcome from toxicity of therapy. The average duration of observation for groups was not indicated and no statistically significant difference was obtained due to the insufficient number of observations [34].

In addition, the study of markers of stem tumor cells CD133 (Prominin 1) and OCT4 (Octamer-binding transcription factor 4), as well as transcription factors STAT3 (signal transducer and activator of transcription 3) and C-MYC (myelocytomatosis viral oncogene homolog), which determines the invasive and metastatic potential of a tumor [32]. Some studies have noted a significant correlation between the expression of CD133 in tumor cells and a higher frequency of metastatic lesions, a lower median of overall survival. A CD133 positive variant was detected in 46 out of 70 (65.7%) patients, in 6 out of 16 (37.5%) in the group with a localized osteosarcoma variant, and in 40 out of 54 (74%) in the group with the primary metastatic osteosarcoma (p = 0.002). The median overall survival rate was statistically significantly lower in the group with a CD133-positive tumor variant (p = 0.000). When conducting the study “Transwell invasion”, a significantly higher invasive potential of the CD133-positive variant of the tumor was established (p <0.05). Real-time PCR established a higher level of expression of OCT4 micro-RNA in a CD133-positive variant of the tumor (p <0.05) [25].

Li J.I. et al. in an experimental model on cell lines showed that about 80% of the cells in the CD133-positive variant of the tumor are in the G0 / G1 phases of the cell cycle (p <0.01). Also, real-time PCR revealed a significantly higher level of expression of the multidrug-resistant gene (MDR1) in the CD133-positive variant of the tumor (p <0.05) [23]. In the works of Tu B. c et al. the significance of activation of the IL6R / STAT3 / p-STAT3tyr705 mesenchymal stem cell signaling pathway to increase the metastatic potential of tumor cells was exemplified by the example of cell lines (Saos 2 and U2-OS). The relationship between the increased expression of p-STAT3tyr705 and the increased expression of the drug resistance markers MRP (multidrug resistance protein) and MDR1 has been established. An increase in sensitivity to doxorubicin, but not to cisplatin, was also noted with inhibition of this signaling pathway [33].

Han G. et al. using cell lines (MG63 and SAOS2) as an example, it was shown that an increase in C-MYC expression leads to activation of the MEK-ERK signaling pathway and an increase in the expression of MMP2 and MMP9, which enhance the invasive and metastatic potential of a tumor [15].

Wu X. et al. investigated the prognostic significance of C-MYC expression in biopsy tumor material in 56 children with osteosarcoma who were treated with methotrexate, cisplatin, adriamycin. Expression of the C-MYC protein was detected in 48 of 56 (85.7%) patients. A statistically significant relationship was established between the presence of C-MYC expression and a decrease in the apoptotic index (p <0.05). In addition, in the group of patients with C-MYC-positive variant of the tumor and the intensity of expression, at 2+ and 3+ a significantly lower 3-year-old OM was established (p <0.05). Consequently, in the works of Tu B., Han G. and Wu X. et al. The significance of transcription factors in the development of drug resistance, invasion and metastasis of the tumor has been established.

Innovative therapeutic approaches are used mainly in patients with metastatic osteosarcoma, relapse and refractory course of the disease. Currently, there are the following key areas: 1) the use of monoclonal antibody preparations; 2) tumor-modifying therapy using nitrogen-containing bisphosphonates; 3) the use of chemotherapeutic drugs affecting various cellular signaling pathways (multi-kinase inhibitors, mTOR inhibitors); 4) the use of drugs that promote the activation of tumor-associated macrophages.

Rossi B. et al. presented the results of a study aimed at determining the expression of VEGF (vascular endothelial growth factor) in a biopsy tumor substrate and in tumor material after neoadvanting chemotherapy (2 courses of MAP) in 16 patients with localized osteosarcoma who received programmed treatment using the SSG XIV protocol. Four levels of expression were evaluated: negative and low - at an expression level <25%, medium - at 25–50% (1+), high - at 50–75% (2+), very high — at> 75% (3+). Medium and high levels of VEGF expression in biopsy tumor material were detected in 11 (6 in medium and 5 in high) out of 16 patients (68.7%). After neoadjuvant chemotherapy and the removal of the primary tumor site, VEGF expression was detected in all samples, and there was an increase in expression in samples that were positive during the initial study.

High and very high levels of expression, increased expression after neoadjuvant chemotherapy were statistically significantly correlated with the localization of the primary tumor lesion in the femur (p = 0.02), with the appearance of local recurrence (p = 0.04) and / or early metastatic lesions in the lungs (p = 0.04), with a fatal outcome from the refractory course of the disease (p = 0.04).

Therefore, the presence of VEGF expression in the biopsy material, an increase in the expression of VEGF after neoadjuvant chemotherapy are factors for poor prognosis of the disease [13]. But this study requires the continuation of the fact that it includes a small number of patients.

Currently, little experience has been gained with the use of the drug buvacizumab in children with osteosarcoma.

Bevacizumab is a partially humanized monoclonal antibody to VEGF - A, IgG1, which realizes its activity through the second type of immunopathological reactions (antibody-mediated complement-dependent cytotoxicity, antibody-mediated cell-dependent cytotoxicity) [15]. Back in 1999, employees of the Memoroal Sloan-Kettering Cancer Center presented the results of a study assessing the effect of ErbB2 expression (erb-b2 receptor tyrosine kinase 2) on the nature of the histological response after neoadjuvant polychemotherapy and on the rates of OS and BSV. The study included 53 patients. ErbB2 overexpression was detected in 42% of patients in the entire study group, in 50% with metastatic variant and in 76% at the time of detection of relapse or refractory course of the disease, and also statistically significantly correlated with a poor histological response (p = 0.02) and BSV (p = 0.05). The 5-year BSV in patients with a localized version of osteosarcoma and ErbB2-positive status was 47%, with ErbB2-negative status - 79% [13].

Conflicting data on the prognostic significance of ErbB2-positive status in patients with localized osteosarcoma were obtained.

In 2002, the Japanese Osteosarcoma Group (Japanese Osteosarcoma Group) published the results of a study that included 155 patients with localized osteosarcoma from 1984 to 1995. At the same time, the 5-year BSV in patients with ErbB2-positive status was 45%, with ErbB2-negative status - 72%.

In 2014, the American Pediatric Oncology Group (COG) presented

completely different results of the study, which from 1999 to 2002 included 135 patients with localized osteosarcoma. Only 13% of patients showed ErbB2-positive status. The 5-year RR in patients with ErbB2-positive status was 73%, with the ErbB2-negative status - 72%, the 5-year RR - 59% and 69%, respectively. No statistically significant difference in survival was observed [14]. Thus, it was confirmed that ErbB2 can be considered as a potential target for targeted therapy for metastatic variant, relapse and refractory course of the disease.

Trastuzumab is a partially humanized IgG1κ monoclonal antibody to ErbB2, which also realizes its activity through a second type of immunopathological reaction (antibody-mediated complement-dependent cytotoxicity, antibody-mediated cell-dependent cytotoxicity). The drug was administered at a dose of 4 mg / kg in the first week, then 2 mg / kg 1 time per week (34 in total) only in patients in whose tumor substrate ErbB2 expression was detected. In the group with trastuzumab, a good histological response was detected in 56% of patients, without trastuzumab - 40%, a poor histological response - 44% and 60%, respectively. At the same time, the 3-year OS and BSV in the group of patients who received treatment with trastuzumab accounted for 59% and 32%, and in the group of patients who received treatment without trastuzumab - 50% and 32%. Consequently, the use of trastuzumab with polychemotherapy MAPIE led to an increase in the frequency of achieving a good histological response, but not to an increase in the rates of OS and BSV [7]. Of particular interest is tumor-modifying therapy using nitrogen-containing bisphosphonates. Currently, the following mechanisms of action of nitrogen-containing bisphosphonates have been identified, which are represented by the activation of tumor cell apoptosis by the caspase mechanism (indirectly through Rb and P53 protein) and without the participation of the caspase mechanism (an increase in AIF — apoptosis of the inducing factor); increased expression of TRAIL-DR5 (TNF-related apoptosis-inducing ligand - death receptor 5, TRAIL - induced apoptosis); a decrease in RANKL expression (Receptor activator of nuclear factor kappa-B ligand - ligand of nuclear factor activation receptor kB) in osteosarcoma cells, which leads to suppression of tumor cell proliferation, osteoclast activity, changes in tumor microenvironment, bone resorption and risk of metastasis; activation of γδT cellular cytotoxicity; activation of the tumor-associated macrophages [23].

At present, a rather small experience has been gained of using these drugs in children with osteosarcoma.

Meyers P.A. et al. published the results of a study on the combined use of pamidronate with MAP chemotherapy. The study included 40 patients, 32 in the age group up to 18 years, 29 with a localized osteosarcoma variant, 11 with a primary metastatic osteosarcoma variant. In accordance with the program, pamidronate was administered once a month at a dose of 2 mg / kg 48 to 72 hours after adriamycin, methotrexate, a total of 12 administrations. Surgical removal of the primary tumor lesion was performed at week 11. Adjuvant chemotherapy started at week 13. Removal of metastatic foci was carried out individually at the stage of adjuvant therapy.

The frequency of achieving a good and poor histological response is not indicated. However, fairly high rates of 5-year OS and BSV were obtained: 93% and 72% in patients with localized osteosarcoma, 64% and 45% in patients with metastatic osteosarcoma [25]. The American Pediatric Oncology Group (COG) presented the results of the pilot protocol AOST06P1 aimed at studying the combined use of zoledronic acid with the polychemotherapy of MAPIE in children with the primary metastatic osteosarcoma. This study included 24 patients. Zoledronic acid was administered at a dose of 1.2 - 3.5 mg / m2 in each course of chemotherapy. Piperno-Neumann S. et al. presented the results of a phase 3 randomized study OS 2006, the purpose of which was to identify the potentiating effect of zoledronic acid when used together with polychemotherapy MIE and MAP.

The study included 217 children, 107 in the control group and 110 in the group with zoledronic acid. Groups of patients were statistically significantly comparable by sex, age, foci of primary and metastatic lesions, and histological variant of the tumor.

Zoledronic acid was administered at a dose of 0.05 mg / kg (maximum dose of 4 mg) with each course of chemotherapy (IE and AP). Neoadjuvant chemotherapy consisted of 2 courses of IE (ifosfamide (I) 12 g / m2, etoposide 300 mg / m2) and 7 administrations of high-dose methotrexate ((M) 12 g / m2). Surgical removal of the primary tumor lesion was performed at week 14. Adjuvant chemotherapy included 2 courses of MIE in the group with a good histological response and 5 courses of MAP in the group with a poor histological response. A good histological response after neoadjuvant polychemotherapy was achieved in 73% of patients. However, there was no statistically significant difference in achieving a good histological response, in terms of OS and BSV in groups of patients who received programmed treatment with or without zoledronic acid. The number of events in the group with zoledronic acid was 42% (47/110), in the group without zoledronic acid - 31% (34/107). Consequently, this study shows the high effectiveness of chemotherapy courses for IE in combination with methotrexate in the neoadjuvant regimen. The presence of the potentiating effect of zoledronic acid has not been proven.

In the treatment of refractory forms of osteosarcoma, drugs are also used that affect various cellular signaling pathways. Understanding the mechanisms of tumor activation opens up the possibility of using multikinase and mTOR (mammalian target of rapamycin complex) inhibitors.

Takagi S. and Peng N. et al. In an in vitro experiment on cell lines (SaOS2, MG63, HOS), pathogenetic mechanisms of cytokine-induced tumor transformation and proliferation were shown through the activation of VEGF / VEGFR / PI3K (Phosphatidylinositol-4,5-bisphosphate 3-kinase) / AKT (Protein kinase B) and the PDGFR (Platelet-derived growth factor receptor) / PI3K / AKT signaling pathways. The most studied drugs from this group are currently sorafenib (nexavar) and everolimus. Sorafenib is a non-selective multi-kinase inhibitor that inhibits the activity of various cellular signaling pathways, in particular VEGFR1, VEGFR2, PDGFRα, PDGFRβ, while everolimus is an mTOR inhibitor. Ymera P. et al. of the Italian Sarcoma Group published the results of a preclinical study (in vitro and in vivo), which noted the mutually potentiating antitumor effect of everolimus and sorafenib on osteosarcoma cell lines (KHOS, MNNG-HOS, U2OS). The effect of everolimus and sorafenib on mTORC1 / mTORC2 is manifested in a decrease in the expression of mTORC1 and an increase in the expression of mTORC2, which provides proapoptotic and antiproliferative effects. With the combined use of everolimus and sorafenib, the expression of both mTORC1 and mTORC2 decreases.

From 2008 to 2009, Grignani G. et al. of the Italian Sarcoma Group conducted a second phase of clinical trials of the drug sorafenib in patients with relapse and refractory osteosarcoma. The study included 35 patients with osteosarcoma

in the age group over 14 years. Partial response was achieved in 5 (14%) patients, disease stabilization in 12 (34%) patients. The overall response rate was 48%. At the same time, 4-month progression-free survival was 45% (15 out of 35).

Thus, taking into account the data of 2008 studies (use of sorafenib in mono mode) and 2011 (using a combination of sorafenib with everolimus), it can be said that the combination of sorafenib with everolimus leads to an increase in the overall response rate, an increase in survival rate without disease progression within 6 months However, by the year this difference disappears.

Compared to international data (Italian sarcoma group) in the presented study, the achievement of a partial response, stabilization of the disease and the overall response rate were significantly higher.

Currently, a number of studies aimed at studying the role of tumor-associated macrophages. Activation of tumor-associated macrophages can be carried out through the use of preparations of liposomal tripeptides (mifamurtid), preparations of interferons (interferon alpha-2A).

Meyers P.A. et al. presented the results of the randomized study CCG 7921 / POG 9351, which was conducted from 1993 to 1997. The study included 662 patients with a localized version of osteosarcoma.

A feature of line A therapy was the use of 2 courses of neoadjuvant chemotherapy for MAP; in the line of therapy B: 2 courses of neoadjuvant chemotherapy MAI, alternating courses of MAR and MAi at the stage of adjuvant chemotherapy. Surgical removal of the primary tumor lesion was performed at week 10. Mifamurtid (MTR) was administered at a dose of 2 mg / m2 2 times a week for 12 weeks, then once a week for 24 weeks according to randomization. The mechanism of action of mifamurtid (MTP) is to activate monocytes / macrophages with antitumor activity, which is realized as a result of binding to specific receptors TLR4 (toll-like receptor 4) and NOD2 (nucleotide-binding oligomerization domain 2 receptor) with a subsequent change in the activity of cellular signal pathways (ERK1 / 2 - extracellular-signal regulated kinase 1/2), NF-kB - nuclear factor kappa-B, AP1 - adapter protein 1). After removal of the primary tumor focus, a good histological response in group A was achieved in 42% of patients, in group B in 48%, a poor histological response in group A - 58%, in group B - 52%. At the same time, the 6-year-old RR was 74%, without the use of MTP - 70%, with the MTR - 78%; BSV - 64%, without the use of MTR - 61%, with MTP - 67%. In group A: OS without the use of MTR - 71%, with MTR - 75%; BSV without MTR -64%, with MTR - 63%. In group B: OS without the use of MTR - 71%, with MTR - 75%; BSV without MTR -64%, with MTR - 63%. The addition of MTP to polychemotherapy led to a statistically significant increase in the 6-year OS from 70 to 78% (p = 0.03), and there was a tendency to an increase in BSV, mainly in group B (p = 0.08) [26].

Kubo T. et al. published the results of a pilot study that determined the prognostic significance of the expression level of interferon α / β receptors in 40 patients with localized osteosarcoma who received treatment according to the NECO95J program. The expression of interferon α / β receptors was detected in 45% of patients. When conducting multivariate statistical analysis, a significant association was observed between the expression of interferon α / β receptors and 5-year-old OM and the survival free of metastatic lesions (VSMP). The 5-year OM, in the presence of expression of the α / β interferon receptor in the tumor substrate, was 81%, with no expression, 47% (p = 0.043), the 5-year HSMP - 75% and 41% (p = 0.023). This study confirms the possibility of using interferon preparations in the treatment of osteosarcoma in patients with overexpression of α / β interferon receptors [12]. Bielack S.S. et al. presented the results of the EURAMOS1 study in patients with a good histological response after neoadjuvant MAP chemotherapy. In the age group up to 30 years, the MAP line of therapy was carried out to 359 patients, the MAP INF line - 2b - to 357 patients, in the age group up to 20 years - 333 (92.7%) and 332 (92.9%) patients. Groups of patients are statistically significantly comparable by gender, age, localization of the primary tumor lesion, the presence of a metastatic lesion, the histological variant of the tumor. In accordance with the program, pegylated INF - α - 2b was administered at a dose of 0.5 mg / kg (at a maximum dose of 50 mg) once a week for 4 weeks, then 1 mg / kg (at a maximum dose of 100 mg) 1 time per week (from 30 to 104 weeks of programmed treatment). In a group of 630 patients with a localized version of osteosarcoma, 135 events were detected, 72 in patients who received the MAP therapy line, 63 in patients who received the MAP INF therapy line - 2b. At the same time, the 3-year BSV was 77% and 80%, respectively. Therefore, the use of INF - α - 2b as a supportive therapy after MAP in patients with a good histological response did not lead to an increase in BSV [6].

Conclusion. Thus, the results of treatment of children with primary metastatic osteosarcoma, relapse and refractory course of the disease remain unsatisfactory. Molecular biological factors that determine sensitivity to chemotherapy, invasive and metastatic potential of the tumor, as well as the prognosis of the disease, among which special attention is deserved: expression of MGMT protein, methylation of the promoter part of the MGMT gene, expression of ERCC1 proteins, VEGF, CD133, p -STAT3tyr705, C-MYC, expression of RFC1 micro-RNA and the presence of rearrangement of the TOR2A gene. It is important to note the following fact that there was no comprehensive assessment of the value of these markers for the histological response to neoadjuvant chemotherapy and survival rates in patients with osteosarcoma.

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POINT OF VIEW

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YAKUTIA'S LONGEVITY PHENOMENON – MYTH OR REALITY

ABSTRACT

In the Soviet years the idea was formed, that Yakutia was one of the centers of longevity in the country. Based on the study of archival materials and census data, it was established that this statement was erroneous. The reasons for spreading this false statement are shown. As an illustrative example, the church and statistical documents of the Oymyakonsky and Suntarsky uluses were considered as areas of Yakutia, where the so-called longevity phenomenon was most pronounced. The age of specific residents of Oymyakonsky district from the family list for 1928 was compared with the lists compiled from 1942 to 1946, as a result of which it was established that in most cases the villagers provided overestimated information about their age.

Keywords: demography, Yakuts, aging, longevity, Yakutia.

In 1897, the first general population census was conducted in Yakutia, the results of which found that 1043 centenarians live in the region, including 90 people aged 100 years or more [9]. In connection with the above, at the end of 1898, the manager of the Central Statistical Committee addressed a letter to the governor of the Yakutsk Oblast V.N. Skripitsyn, asking to provide detailed information about each resident of Yakutia who had crossed the centenary: *"... A special survey is required about each one, in the ways of understanding all their living conditions and the accuracy of the age shown ..."* [16]. Attached to the letter were 50 copies of questionnaires with 38 questions regarding the respondent's lifestyle, physical condition, and heredity.

On February 15th, 1899, by order of the governor, 10 questionnaires were sent to the Yakutsk Oblast District Police Officer, Olekminsky – 12, Vilyuisky – 4, Verkhoyansk – 5 [18]. Later it turned out that when filling them, the age of 19 surviving respondents living in the districts by that time was recorded from hearsay, in connection with which Skripitsyn demanded additional confirmation: *«…I consider it a good practice – in all 19 cases – to ask local clerks to verify the validity of testimony at the age using metric records and, if it is impossible to extract data from the birth records, then trace the testimony of age at confessions and marriage records. In the absence, for any reason, of a second copy of these books at the priests, detailed information will be needed about the time for the provision of metric books to the spiritual consistory with the exact designation of the name of the parish…»* [17].

Although the search continued for more than 2 years, in most cases it was impossible to establish the exact date of birth. This was mainly due to the lack of information about these people in church documents, since many parishes appeared later than the date of birth of the respondent. But in the case when it was possible to establish the necessary information, it turned out that the respondent was much younger than expected. So, at that time, the oldest of the verified centarian of Yakutia was 94-year-old Anna Ivanova Maksimova from the Vilyui District [19], while the rest of the "aged" were 70-80 years old. In this regard, a rather indicative was the letter of the Zemstvo Assessor of the 3rd District of the Yakutsk Oblast dated December 10th, 1901 addressed to the District Police Officer of the Yakutsk Oblast*: «…I received the honor of submitting information about the three elderly persons of Dyupsinsky Ulus and informing you that according to the attached certificates of confessional books, these persons in the year of the general census were not 100 years old, but much less – they were Matrena Ivanova Dmitrieva (according to the confessional book: Matveyeva), only 72 years of age; Anisye Ivanova Ushnitskaya (according to the confessional book: Matrena Ushnitskaya) is only 73 years old, and Kapiton Porokhov is only 76 years old. These certificates from confession books are given by clerks and deserve more confidence than the testimony given during the census, since the Yakut who can remember their years well are is more likely an exception, in most cases Yakuts tend to lose count of their years and continue the counting according to presumptive and major figures, for example: "Min (*Yakut for