BISPHOSPHONATES IN TREATMENT OF BONE SARCOMAS

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Summary

Theanalysisoftheeffectivenessofthecombinationofchemotherapyandbisphosphonatesintreatmentofbonesarcomas was performed. This article presents the results of our research on the therapeutic effect of bisphosphonates. We have assessed the impact of bisphosphonates on pathomorphosisof malignant bone tumors, stability and durability of the reconstruction after surgical resection of bone. The safe use of antiresorptivetreatment in combination with chemotherapy is proven. The data analysis suggests that bisphosphonates improve efficiency of treatment of bone sarcoma without increasing the toxicity of the treatment.

Key words: bisphosphonates, primary malignant bone tumors, stability of limb reconstruction.

Studies of past years have proved the effectiveness of a number of cytostatic agents in the treatment of bone sarcomas. Nowadaysthere is a clear algorithmof treatment of malignant bone tumors. The golden standard treatment of these diseases consists of neoadjuvant chemotherapy, radical surgical resection and adjuvant chemotherapy. List of medications included in this algorithm is well-known, is rather limited and include methotrexate, cisplatin, doxorubicin, ifosfamide and etoposide. Despite the rapid development of the pharmaceutical industry, a list of first-line drugs in the treatment of sarcomas of bone remains the same. Attempts to use targeted drugs do not achieve the desired results [1, 2]. Treatment ofthepatients with chemoresistant forms of malignant bone tumors remains an unsolved problem and require a totally new approach to therapy. [3] This group of patients pushes researchers to search for new approaches and methods of treatment.

By studying the bisphosphonates (BP), which had worked well earlier in oncology practice in the treatment of metastatic bone lesions, we hypothesized that they may have an effect on the primary malignant bone tumor process. This effect was confirmed by some of the world's researches [4, 5].

BF is a group of medications that inhibit the pathological bone resorption. Due to features BP, they are widely used in oncology practice, as have antiresorptive, antiangiogenic and antineoplastic effect [6]. It was believed that the mechanism of action of BP was directed at stabilizing the bone. BP directly affect the tumor cells in patients with multiple myeloma [7, 8, 9, 10].

Numerous studies support the hypothesis that BF is an active against of osteosarcoma, alone or in combination with chemotherapy. The effect of alendronate, clodronate, ibandronate, pamidronate and zoledronate for osteosarcoma in animals, as well as the culture of human osteosarcoma cells was assessed[11-21].

Known as the fact that a large number of patients with primary bone sarcomas are treated with a course of chemotherapy, carry fractures during

treatment [22]. For these patients, there is a risk of osteoporosis and pathological fractures of the continuation of their lives. Bone resorption is a recognized problem for young patients receiving chemotherapy. For adults with osteoporosis, treatment with BP reduces the number of fractures by 50% after 1 year of treatment. In these patients, an increase in bone mass was 4.2% per year during the first 4 years of treatment. Even more dangerous for this group of patients are pathological fractures in the area of the tumor, which may affect the survival and local recurrence. Various scientific reviews stated that the rate of 5 years survival in patients with osteosarcoma and pathological fracture is 55%, and patients with osteosarcoma without fractures - 77%. Number of local recurrence is also increased in the group with pathologic fractures (25% vs. 4%). [22]

Analyzing all the preliminary data we can state that BP are a completely new approach in the treatment of malignant bone tumors, but their use is not an alternative to conventional treatment as an independent method, and can only be used in combination with chemotherapy.

The aim of our study is to estimate the efficacy of BP in combination with chemotherapy in the treatment of patients with primary malignant bone tumors, to determine whether the combination of chemotherapy and BP increase or decrease the toxic effects of treatment,to assess the effectiveness of BP to prevent instability of implant [23-27].

Materials and methods

In 2009, the National Cancer Institute and the Institute of Spine and Joint Pathology named after M.I.Sitenko started a randomized multicenter trial to study the effect of BP in combination with chemotherapy in the treatment of primary malignant bone tumors.

Criteria for inclusion in the study:

• morphologically confirmed diagnosis of all histological types of primary malignant bone tumors that have not been treated;

• patients with only local forms of low-grade sarcomas (IIA, IIB).

The study included 47 patients with different clinical forms of bone sarcomas. Patient's age - from 18 to 55 years; 22 – women, 25 - male. Characteristics of patient groups are presented in Table 1 and 2.

Table 1. Structure of groupsof patients

Characteristicsofpatients		Main group (n=18)		Group of control (n=29)	
		n	%	n	%
Sex	**Male**	10	55,5	15	51,7
	Women	8	44,5	14	48,3
Age, years	**18–30**	9	50,0	16	55,2
	31–50	7	38,9	9	31,0
	> 50	2	11,1	4	13,8
Tumor	**of limb**	17	94,5	27	93,1
	of pelvis	1	5,5	2	6,9

Table 2. The distribution of patients according to the morphological diagnosis and location of the tumor

	Location									
	Femur		Tibia		Humerus		Pelvis		Total	
	n	%	n	%	n	%	n	%	n	%
Osteosarcoma	22	46,8	3	6,4	1	2,1	1	2,1	27	57,5
Fibrosarcoma	4	8,5	1	2,1	-	-	-	-	5	10,6
Malignant giant cell tumor	1	2,1	3	6,4	-	-	-	-	4	8,5
Malignantfibroushistiocytoma	2	4,2	3	8,5	1	2,1	-	-	6	12,8
Angiosarcoma	1	2,1	-	-	-	-	1	2,1	2	4,2
Mesenchymalchondrosarcoma	1	2,1	1	2,1	-	-	1	2,1	3	6,4
Total	31	66	11	23,4	2	4,2	3	6,4	47	100

Byrandomization, all patients were divided into two groups, depending on the useof BP, formingthe main andthe control group.The study

groupincluded18patients whowerereceivingastandardtreatment (neoadjuvant chemotherapy, radical surgicalresection,adjuvantchemotherapy).The control group consistedof 29 patientswho were treatedaccording to thesamescheme, butwith a monthlyinfusionofBP.The results were evaluatedby the following criteria: clinical tumor responsetotherapeutictreatment, comparison of therapeuticpathomorphism, implantstabilityandtoxicity.

All patients underwent a standard treatment algorithm that includes neoadjuvant chemotherapy, surgical treatment in the amount of bone resection followed by displacement of defect with implant and adjuvant chemotherapy, which depends on the response to preoperative treatment. Preoperative chemotherapy (endoarterial) started with cisplatin in a course dose 120 mg/m^2 (2 infusions of 60 mg/m^2 for 2 - 3 hours), with pre-and posthydration. At the 3-4th day, the patient received doxorubicin 75 mg/m^2per course (intravenous infusion for 2 to 4 hours). At day 21 - 4-hour intravenous methotrexate of 12 g/m^2supported by infusion therapy with concentration measurement after administration, and then every 24 hours (more frequently if necessary). A day leucovorin in a dose of 15 mg/m2 every 6 hours was administredto reduce the concentration of methotrexate in plasma and 0.2 micromoles/l. Infusion therapy was based on 2000 ml/m^2 of fluid per day, was administered 1 hour before methotrexate infusion for 36 hours, to maintain the electrolyte balance and constant alkalinity of urine (pH> 7). Infusion was corrected individually depending on toxicity and complications. Measurement of the concentration of methotrexate in plasma was carried out on TDxanalizer (Germany).

For each patientwe provided threechemotherapycyclesusing3medications every 3 weeks. After limb-sparing surgery the adjuvant chemotherapy was administered: methotrexateat the same dosage, and, followingaoneweekcisplatinof150 mg/m^2course dose (48-hour continuous administration) and doxorubicin, administered 21 days after thecisplatinata dose of 90mg/m2 (two-fold 4-hourintroduction).Cycleswererepeatedevery 3weeks.The number of cycleswas determined by

thedegreeofpathomorphismafterAvtandilovandHuvosgraduation[28-30]:2 cycles-at1st degree(100%tumor necrosis), 3-4 cycles - atthe 2nddegree(from 91% to 99.9%necrosis).In case of badpathomorphismafter treatment (90% and below - 3–4thdegree) the treatment regimenalsoincludedifosfamideina dose of 12g/m2 (3 courses).

In the main grouppatientsreceivedmonthlyintravenousinfusionofBPat a standard dose.Weusedmainlypamidronate (10) andibandronate(8).

Pamidronatewasusedat a dose of60 mgforpatientsweighing up to60 kg,and 90mg forpatientsweighingmore than 60kg.Ibandronatewas usedat a dose of6 mg.Thetimebetween the application ofBPandcisplatinormethotrexatein high dosesshould be at least24 hours.BPwereadministeredonceamonth,a total of 12doses.The patient receivedthe first dosein the first cycleofchemotherapy.Pamidronatewasadministeredas a 2-hour infusion, ibandronate–as 15 minute infusion.

Surgical treatment

In the study, most patients underwentlimb-sparingsurgicalremovalof the tumorwith the installationofan implant.

In our study,radicalsurgerywas performed in47 patients.Typeofsurgerydepended on thelocation and extentof the main process, the presence of metastatic disease, the future growth ofthe patient.2amputations, 4 resectionsofdefectautograftand 35resectionsfollowedby installation of cement-basedimplant were performed (Table 3).

Table 3. The distribution of patients according to surgical treatment

Вид хирургическоговмешательства	Количество пациентов, n
Bonetumorresection+knee arthroplasty	35
Bonetumorresection+ankle arthroplasty	1
Bonetumorresection+hip arthroplasty	1
Bonetumorresection+shoulderjointarthroplasty	4
Bonetumorresection+autograftreplacement	4

Amputation	2
Total	47

Wehaverecommended to perform the movementsin the operatedjointwitharthroplasty on the second dayafter the operation.Grossaxleloadon a limb was permittedin 3 weeks.We have performed reoperationsin order tofixateintramedullarypins, due to severity of pain,in patients with radiographic signsof aseptic implant instability.

Results anddiscussion

Wehaven'tevaluatedthesurvivalof patients because ofthe short duration offollow-up.Themaincriterion for evaluatingthe antitumor activityofBPwas to compare theamountofviable tumor cellsbyHuvoscriteria.

the effectofBPwasalso evaluatedbyclinical data(pain), X-ray (restoration ofcorticalbone structure, the phenomena of ossificationin the area of politicaldestruction, stabilization of pathologic fracture), and bythetoxicityin both groupson a scale ofECOG.In the group ofpatients treated withBP,the severity of painwas significantly reducedby an average24 hours afterthe first administrationofBP,in the control group, this effect occurs later(after an average of 5 daysafter the start oftherapy).Preliminary resultsare presented in Table4 andFigure 1.

Table 4.The distribution of patients according to the results of treatment.

	Main **(n=18)**		Control **(n=29)**	
	n	%	n	%
Good pathomorphosis	15	83,3	18	62,1
Toxicity after	10	55,6	11	38,0

ECOG above 3				
Implant instability	0	0,0	5	17,3

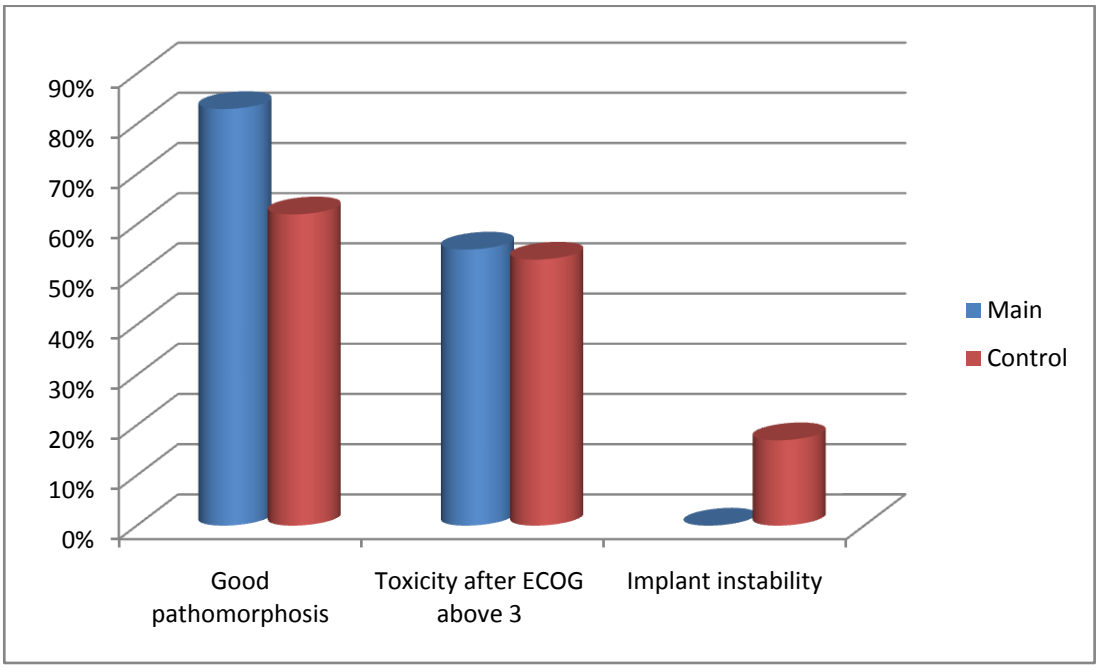


Fig. 1. The distribution of patients according to the results of treatment

Inthe control group,severepainoccurred in 7 patients,whichwasassociatedwith the appearance ofthelineas a signasepticlooseningofprosthesis pins(Fig. 2). 4 of the patientswho did not receiveBPunderwent reoperations in order to reinstall pins of an implant.

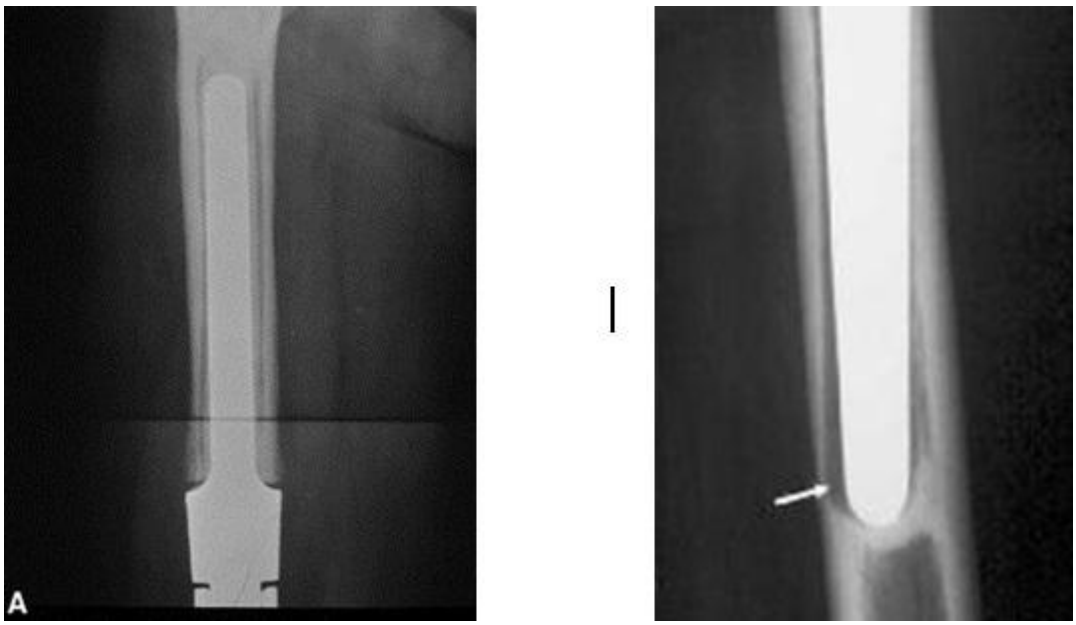
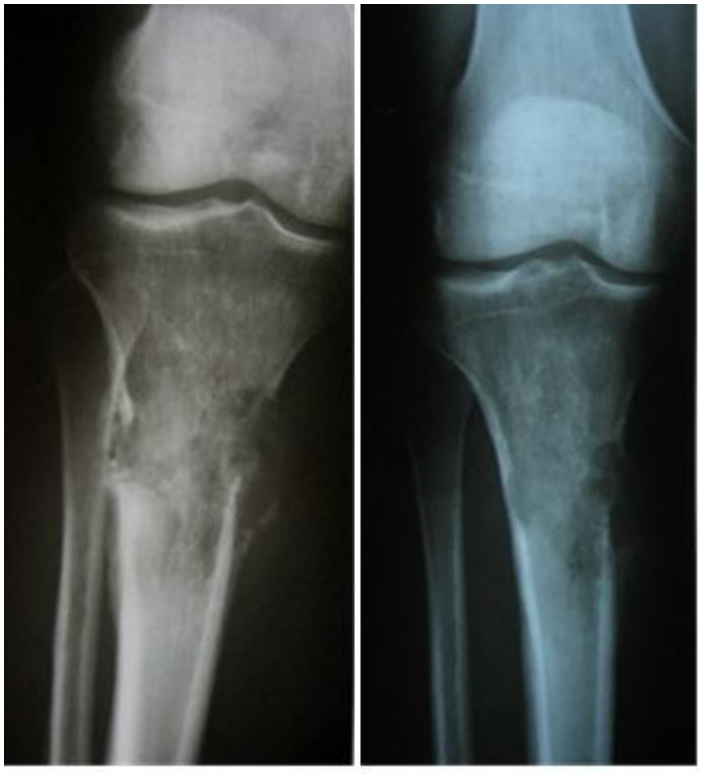


Fig. 2.Line on X-ray: aseptic loosening of prosthesis pins.

And to assess theeffectof BP we comparedradiographsofpatientsin the dynamicsinthe main and controlgroups.Ossificationin the zoneofdestructionwas observed in100% of patientsin the first groupand 40%- in the second(Fig.3).



а) **б)**

Fig. 3.Bone destruction: a) prior to the treatment, b) after the treatment.

One of the most important issues in our study was to evaluate the safety of BP, as during chemotherapy toxic drugswere used. Toxicity assessment was performed on a scale of ECOG. Particular attention was given to displays of nephrotoxicity, hepatotoxicity, hypocalcemia and occurrence of osteonecrosis of the mandible. We compared the expression and manifestation of toxicity in the main group and the control by monitoring key laboratory parameters: hypocalcemia, the dynamics of hemoglobin, white blood cells, platelets, creatinine clearance, the dynamics of transaminases, bilirubin. clinical manifestations of toxicity were also evaluated: nausea, vomiting, diarrhea, stomatitis, allergic reactions (Table 5).

Table 5.A comparison ofthetoxicityof the treatment

Toxicity criteria	Toxicity level ≥ 3			
	Control group, 29		Maingroup, 18	
	n	%	n	%
Leukopenia	12	41,4	10	55,6
Neutropenia	25	86,2	15	83,3
Thrombocytopenia	18	62,1	10	55,6
Hyperbilirubinemia	5	17,3	2	11,1
Transaminases ↑	7	24,1	3	16,7
Diarrhea	2	6,9	0	0,0
Nausea	27	93,1	18	100,0
Vomiting	25	86,2	15	83,3
Stomatitis	16	55,2	12	66,7
Proteinuria	0	0,0	0	0,0
Hematuria	0	0,0	0	0,0
Pulmonitis	0	0,0	0	0,0
Hyperthermia	3	10,3	2	11,1
Allergic reactions	2	6,9	1	5,6

Skin reactions	2	6,9	1	5,6
Infection	5	17,2	3	16,7
Dysfunctionoftheheart	0	0,0	0	0,0
Neurotoxicity	0	0,0	0	0,0
Pain	20	68,9	10	55,6
Agomphiasis	0	0,0	0	0,0
Hypocalcemia	0	0,0	4	22,2

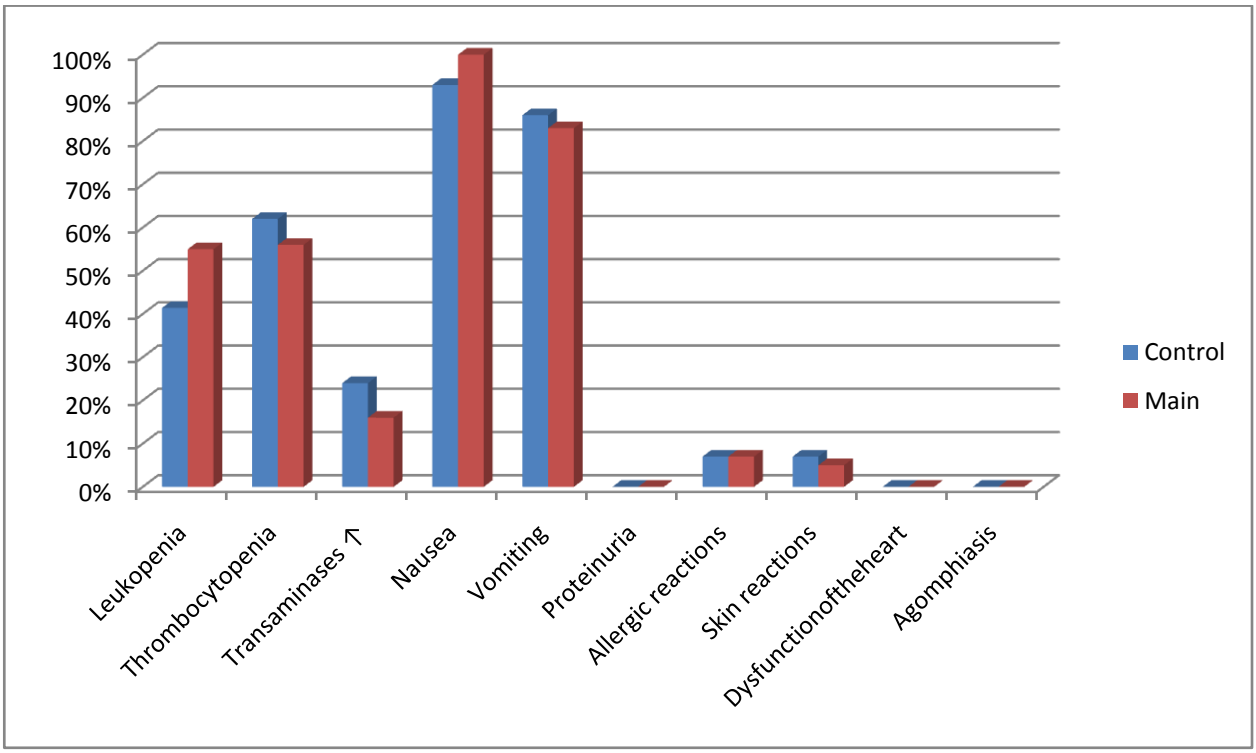


Fig. 4. A comparison of the toxicity of the treatment

There wasn't any cases of osteonecrosis of the jaw at the time of treatment, or during the period of observation.

Comparing the results, we found that toxicity of chemotherapy does not depend on the use of BP. Our experience with BP and chemotherapy in the treatment of malignant bone tumors suggests that the oncologist can safely and effectively combine BPwith chemotherapy.

Most patients tolerated BP. The most common adverse events were flu-like symptoms (fever, arthralgias, myalgias, and bone pain), fatigue, weakness, and

reaction from the gastro-intestinal system. These symptoms were usually mild, quickly ceased and did not require medical treatment.

BP therapy can improve the durability of the prosthesis through different mechanisms, including:

• improve the density and strength of bone;

• promote more reliable ingrowth into porous surfaces of non-cement prosthesis;

• stabilization of the connections of the bone-prosthesis or bone-cement slowing the osteoclastic bone resorption.

Own experience with BP in combination with cytotoxic drugs for the treatment of bone sarcomas, as well as an analysis of numerous studies give reason to say that the BP can be safely used in combination with chemotherapy and are a new effective therapeutic approach to the impact of malignant bone tumors. BP give an opportunity to improve the stability and durability of the reconstruction after surgical resection of bone, which would reduce the number of repeated surgeries.

Undoubtedly, the use of BP in the treatment of sarcomas of bone remains at the stage of experience. However, even at this stage, we see strong evidence of their effects that contribute to the effectiveness of treatment of cancer patients. Safe use of BP is proved and confirmed by multicenter studies, making them available in clinical practice. The study shows the effectiveness of therapy in comparison with previous experience. BP can increase longevity of prosthesis. These facts give us the opportunity to further studyBP as the addition to the treatment of primary malignant bone tumors.

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