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OSTEOSARCOMA OF THE SPINE — MODERN CLASSIFICATION, THE ROLE OF THE mTOR SIGNALING PATHWAY, PROSPECTS FOR THERAPY (LITERATURE REVIEW)

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Abstract. Despite their rare occurrence, spinal tumors pose a serious problem for public health due to the difficulty of their diagnosis and treatment. Neoplasms of the spine are divided into primary and secondary tumors (metastases) by origin. Osteosarcoma is of great interest among primary tumors. Osteosarcoma is a malignant osteogenic tumor consisting of neoplastic cells that produce osteoid. Osteosarcoma of the spine develops quite rarely, however, it is characterized by a high degree of malignancy, local aggressiveness, a tendency to metastasis, as well as a long asymptomatic course. The prognosis for osteosarcoma of the spine remains extremely unfavorable. All this indicates the need to develop new methods and treatment regimens for osteosarcoma. One of the promising areas is the development of drugs that affect the intracellular signaling pathway mTOR. mTOR is a serine/threonine protein kinase that forms a catalytic subunit of two different protein complexes: mTORC1 and mTORC2. It has been established that this signaling pathway regulates the processes of vital activity of the cell and the entire organism at the deepest level. Its hyperactivation plays an important role in carcinogenesis, including in the pathogenesis of osteosarcoma. In this regard, it was proposed to use drugs that affect the mTOR signaling pathway for its therapy. Such drugs include: rapamycin, everolimus, temsirolimus, catalytic inhibitors of mTOR (MLN0128 and PP242), micro-RNA (miR-223 and miR-101), oleanolic acid, spautin-1, metformin and so on. It is proposed to combine these drugs with classical chemotherapy to achieve better results in the treatment of osteosarcoma. At the moment, it is necessary to select rational combinations and dosages of drugs.

Keywords: osteosarcoma of the spine, mTOR signaling pathway, mTORC1, mTORC2, rapamycin, autophagy inhibitors, metformin, catalytic inhibitors of mTOR, PP242, classification of spinal neoplasms

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ОСТЕОСАРКОМА ПОЗВОНОЧНИКА — СОВРЕМЕННАЯ КЛАССИФИКАЦИЯ, РОЛЬ СИГНАЛЬНОГО ПУТИ mTOR, ПЕРСПЕКТИВЫ ТЕРАПИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Несмотря на редкую встречаемость, опухоли позвоночника представляют серьезную проблему для здравоохранения по причине сложности их диагностики и лечения. Новообразования позвоночного столба в зависимости от происхождения подразделяются на первичные и вторичные опухоли, или метастазы. Среди первичных опухолей большой интерес вызывает остеосаркома, которая представляет собой злокачественную остеогенную опухоль, состоящую из неопластических клеток, которые продуцируют остеоид. Остеосаркома позвоночника развивается довольно редко, однако характеризуется высокой степенью злокачественности, местной агрессивностью, склонностью к метастазированию, а также длительным асимптомным течением. Прогноз при остеосаркоме позвоночника остается крайне неблагоприятным. Все это говорит о необходимости разработки новых методов и схем терапии остеосаркомы. Одним из перспективных направлений является разработка препаратов, воздействующих на внутриклеточный сигнальный путь mTOR. mTOR представляет собой серин / треониновую протеинкиназу, которая образует каталитическую субъединицу двух различных белковых комплексов: mTORC1 и mTORC2. Установлено, что данный сигнальный путь регулирует процессы жизнедеятельности клетки и всего организма на глубочайшем уровне. Его гиперактивация играет большую роль в канцерогенезе, в том числе в патогенезе остеосаркомы. В связи с этим было предложено использовать препараты, влияющие на сигнальный путь mTOR, для ее терапии. К таким препаратам относятся: рапамицин, эверолимус, темсиролимус, каталитические ингибиторы mTOR (MLN0128 и PP242), микро-РНК (miR-223 и miR-101), олеаноловая кислота, спаутин-1, метформин и т.д. Предлагается комбинировать данные препараты с классической химиотерапией для достижения лучших результатов в лечении остеосаркомы. В настоящий момент необходим подбор рациональных сочетаний и дозировок препаратов.

Ключевые слова: остеосаркома позвоночника, сигнальный путь mTOR, mTORC1, mTORC2, рапамицин, ингибиторы аутофагии, метформин, каталитические ингибиторы mTOR, PP242, классификация новообразований позвоночника

BACKGROUND

Spinal tumors remain a serious problem for public health care, which, despite their rare occurrence, are characterized by extreme complexity of their diagnosis and treatment. Thus, vertebral column neoplasms are diagnosed annually in 2.5–8.5 cases per 100,000 population, which is naturally much less frequent than degenerative-dystrophic diseases and traumas [1, 2]. In this regard, specialists often do not consider them as a possible reason for a patient's treatment. This lack of oncological caution may lead to delayed correct diagnosis and, consequently, to a later start of therapy [1].

The main method of treatment of spinal neoplasms remains surgical intervention, supplemented with chemotherapy and radiation therapy if the malignancy of the tumor is confirmed [3, 4]. The complex anatomical structure of this region requires the surgeon to have knowledge not only in traumatology and orthopedics, but also in neurosurgery, neurology, oncology, etc. A related issue is spinal cord tumors [5].

All the above-mentioned points to the significance and relevance of this problem, as well as the need to search for new methods of therapy of spinal neoplasms.

CLASSIFICATION

Spinal neoplasms are subdivided by origin into primary and metastatic (secondary neoplasms). Primary non-lymphoproliferative neoplasms of the spine account for about 5% of all bone tumors (excluding hemangiomas) [4, 6], and in turn are subdivided into benign and malignant neoplasms.

Benign neoplasms of the spine include enostosis, osteoid osteoma, osteoblastoma, aneurysmal bone cyst, osteochondroma, giant cell tumor (osteoblastoclastoma), vertebral hemangioma, notochord cell tumor, pneumatocyst, and Schmorl's cystic nodule [1, 7].

Enneking staging characterizes the activity of benign neoplasms. Stage 1 — latent, stage 2 — active and stage 3 — aggressive [8].

Malignant neoplasms of the spine are divided into nonmyeloproliferative — chondrosarcoma (7–12% of the total number of malignant neoplasms of the spine), Ewing sarcoma (8%), osteosarcoma (3–14%), chordoma (20%), and myeloproliferative — multiple myeloma, solitary plasmacytoma, lymphoma [4, 9].

The degree of malignancy, spread and presence of metastases determines the stage of malignant neoplasms according to Enneking. According to the stage, the type and volume of treatment are chosen [1, 8].

Secondary neoplasms account for about 96% of the total number of spinal tumors. The incidence of metastatic lesions of the spine in disseminated malignant neoplasms is very high. For breast cancer it is 68–74%, for prostate cancer it is 60–68%, for lung cancer it is 40–50%, for thyroid cancer it is 36–42%, for kidney cancer it is 35%, for salivary glands and ENT organs it is 12–22%, for bladder cancer it is 16%, for esophagus and stomach cancer it is 13%, for pancreas cancer it is 6–12%, for colon cancer it is 9%, for cervix and uterine body cancer it is 9%. Melanomas, lymphomas, and sarcomas metastasize to the spine less frequently [10, 11].

Classification of spinal neoplasms by origin and their Enneking staging are presented in Figure 1.

The localization and degree of tumor spread are described by the "Weinstein-Boriani-Biagini surgical staging system" [12], as well as the "surgical classification of spinal tumor lesions according to K. Tomita" [13] (Fig. 2).

Spinal cord tumors deserve special attention. In relation to the spinal cord and its membranes, tumors are divided into three groups:

- intradural intramedullary - those located in the thickness of the spinal cord;
- intradural extramedullary tumors, which lie outside the spinal cord and inside the dura mater;
- extradural tumors located outside the dura mater [14].

Sometimes tumors growing from vertebral column masses or surrounding tissues, when they penetrate the spinal canal and compress the spinal cord, are also referred to as extradural spinal cord tumors [5].

In relation to the length of the spinal cord, neoplasms of the cervical, thoracic, lumbar, and sacrococcygeal sections are distinguished. Craniospinal tumors and cauda equina tumors are distinguished separately [5] (Fig. 3).

PRIMARY NEOPLASMS OF THE SPINE

Primary neoplasms of the spine have different histogenesis. There are tumors of bone, fat, fibrous, nervous tissue, nerve sheaths, adjacent paravertebral soft tissues, and lymphatic vessels [4, 15].

As mentioned above, primary spinal neoplasms are quite rare compared to secondary neoplasms and account for only 4% of the total number of spinal tumors, but benign primary tumors are often asymptomatic, so their true prevalence is unknown. Malignant primary neoplasms are characterized by high local aggressiveness and have the potential to metastasize, which further emphasizes the relevance of the problem [1, 4, 10, 11].

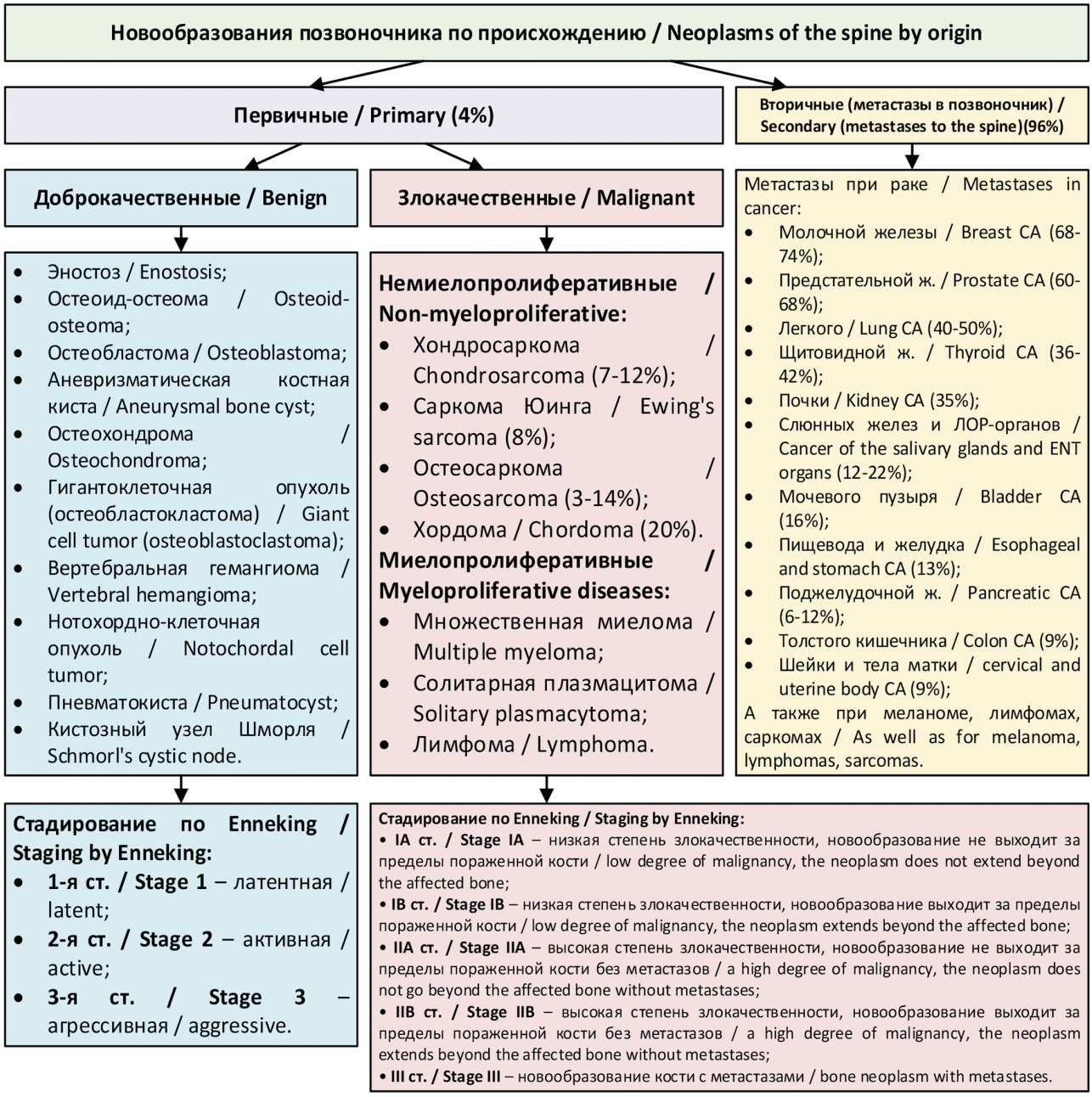

Fig. 1. Classification of spinal neoplasms by origin. CA — cancer

Рис. 1. Классификация новообразований позвоночника по происхождению

Nevertheless, the improvement of imaging techniques and the development of surgical technologies have made it possible to achieve significant progress in their diagnosis and treatment [16, 17]. In particular, surgical interventions on the spine, whether radical tumor removal or palliative surgeries, reliably reduce the severity of pain syndrome and neurological deficit caused by compression of the spinal cord and spinal nerve roots, which significantly improves the quality of life of patients. In addition, the mandatory task of surgeons is to restore the stability of the affected spinal-motor segments [18].

OSTEOSARCOMA

Osteosarcoma is a malignant osteogenic tumor consisting of neoplastic cells that produce osteoid or a substance histologically indistinguishable from it in at least one field of view [19].

The morphologic classification of osteosarcomas according to the “International Classification of Diseases — Oncology (WHO, 2017)” is quite complex and is presented in Table 1 [20].

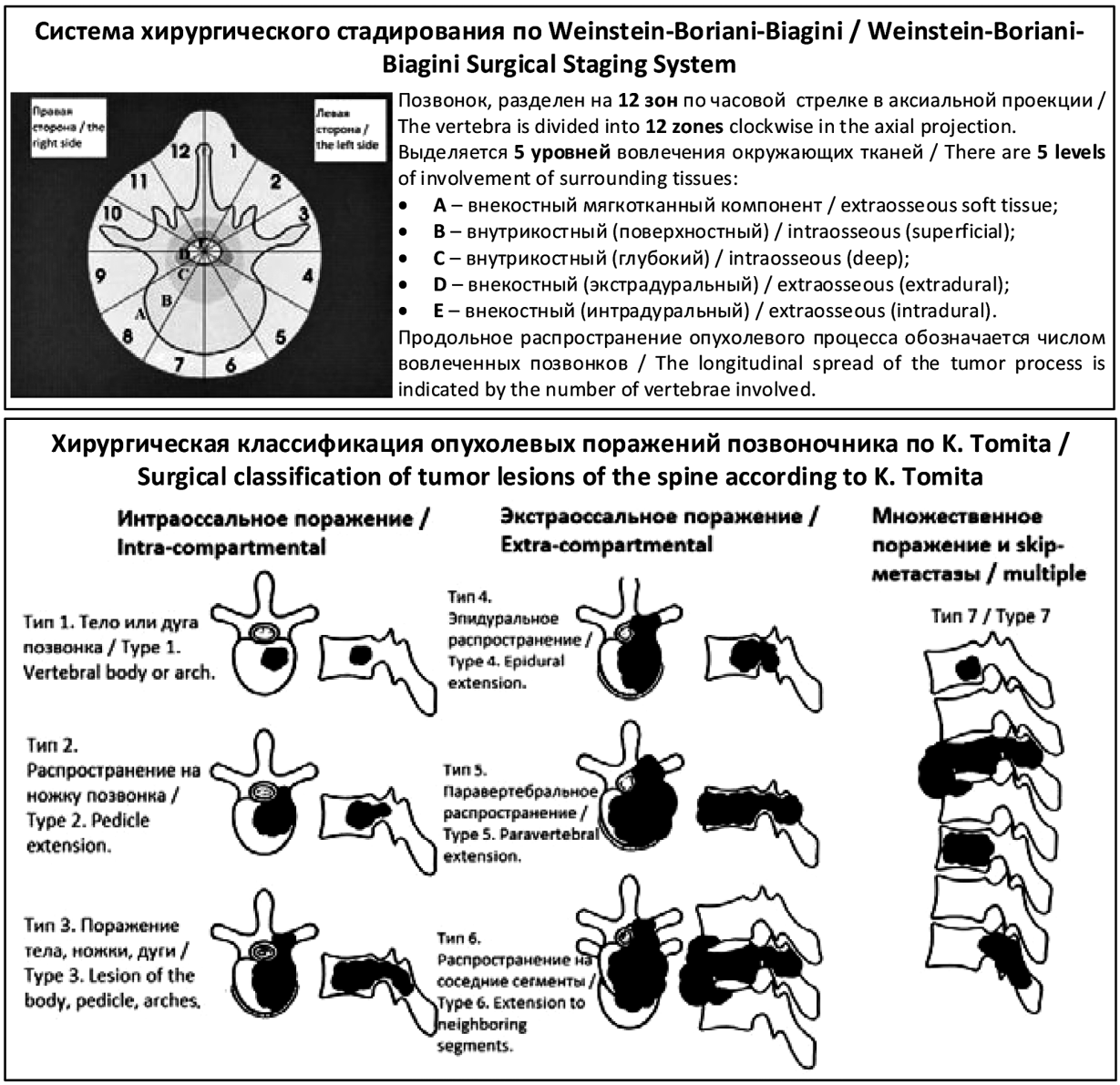

Fig. 2. Classification of spinal neoplasms by localization and degree of spread

Рис. 2. Классификация новообразований позвоночника по локализации и степени распространения

In accordance with the International Classification of Diseases — Oncology (ICD-O), each neoplasm is also assigned a topographic index, and two indices are used for osteosarcomas: C40 - bones and articular cartilage of limbs and C41 — bone and articular cartilage of other and unspecified sites. For example, a neoplasm of the tibia corresponds to the index C40.2.

More convenient for clinicians is the classification given in his works by Dr. E.R. Musaev, corresponding member of the Russian Academy of Sciences. According to this classification, the following subvariants of osteosarcomas are distinguished: by the degree of malignancy — high and low; by localization — central, para-osteal and periosteal; by cell type — osteoblastic, chondroblastic, fibroblastic and so on; by etiology, radioinduced osteo-sarcomas, osteosarcomas on the background of Paget's disease, as well as osteosarcomas of unidentified etiology are distinguished [4] (Fig. 4).

Osteosarcoma is characterized by a high degree of malignancy and unfavorable prognosis, but it develops quite rarely. In the structure of all malignant neoplasms developing in the population, osteosarcoma of any localization accounts for less than 0.001% [19, 21]. Osteosarcoma of the spine, in turn, accounts for about 2% of all osteosarcomas and from 3 to 14% of malignant tumors of the spine [1, 4].

More often this tumor localizes in the lumbosacral region and involves the vertebral body in 90% [22]. Osteosarcoma

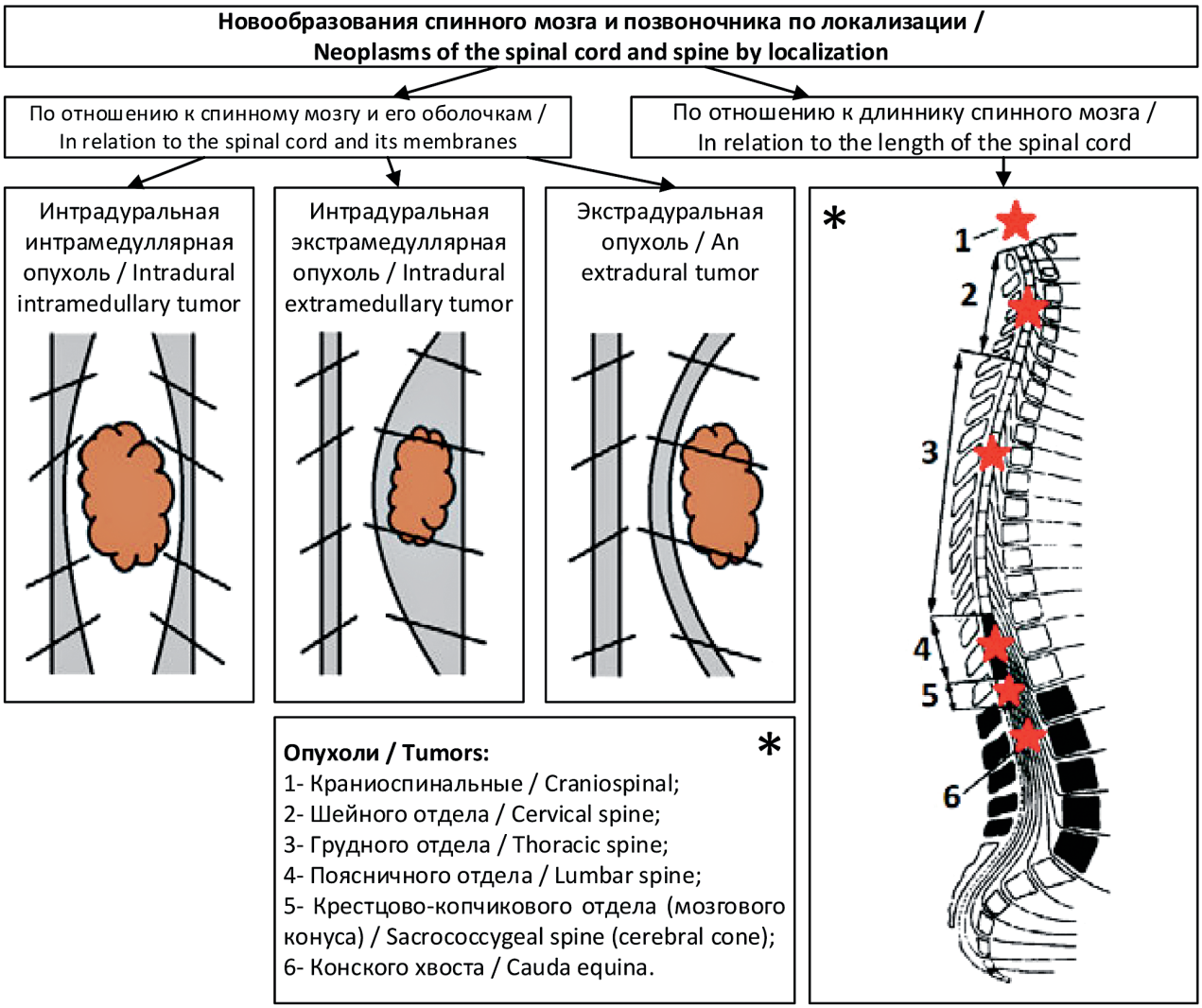

Fig. 3. Classification of tumors of the spinal cord and spine by their localization

Рис. 3. Классификация новообразований спинного мозга и позвоночника по их локализации

generally has a bimodal age distribution. The first peak is seen in the age group of 10–14 years and the second peak is seen above the age of 40 years [19]. However, unlike osteosarcoma of the extremities, osteosarcoma of the spine occurs at older ages [4].

Due to the high degree of malignancy, the generally accepted standard of surgical treatment of osteosarcoma is considered to be its radical removal *en bloc*, which provides significantly better local control compared to intratumoral removal [23].

Preoperative chemotherapy is a mandatory component of treatment [24]. Osteosarcoma is considered a tumor conditionally sensitive to chemotherapy [25]. Radiosensitivity of the tumor is low, but radiation therapy may be administered in case of incomplete removal or lump removal of the tumor [4, 23].

The prognosis of osteosarcoma depends on a large number of factors, including the patient's age and gender, tumor size, presence of metastases, radicality of surgery, stage, levels of alkaline phosphatase and lactate dehydrogenase enzymes, tumor response to preoperative chemotherapy, etc. [19, 24].

To a large extent, the prognosis depends on the localization of the tumor; thus, while in localized distal lesions of long tubular bones in combination with radical resection the 5-year survival rate is more than 80% [19], in osteosarcoma of the spine the prognosis remains extremely negative due to the complexity of radical intervention. According to some data, in a group of 22 patients with osteosarcoma of the spine, the median survival rate was only 23 months [4, 19, 24].

Therefore, there is a need to develop new drugs and treatment regimens for osteosarcoma that would improve the prognosis and increase the survival rate of patients. One of the promising directions is the development of drugs that affect the intracellular mTOR signaling pathway.

Table 1

Morphological variants of ostesarkom in accordance with the International Classification of Diseases — Oncology (WHO, 2017) [20]

Таблица 1

Морфологические варианты остесарком в соответствии с Международной классификации болезней — онкология (ВОЗ, 2017) [20]

Новообразование / Neoplasm	Морфологический индекс / Morphological index
Остеосаркома, БДУ / Osteosarcoma, NOS Остеогенная саркома, БДУ / Osteogenic sarcoma, NOS Остеобластическая саркома / Osteoblastic sarcoma Остеохондросаркома / Osteochondrosarcoma	9180/3
Хондробластическая остеосаркома / Chondroblastic osteosarcoma	9181/3
Фибробластическая остеосаркома / Fibroblastic osteosarcoma Остеофибросаркома / Osteofibrosarcoma	9182/3
Телеангиэктатическая остеосаркома / Telangiectatic osteosarcoma	9183/3
Остеосаркома при болезни Педжета костей / Osteosarcoma in Paget's disease of bones	9184/3
Мелкоклеточная остеосаркома / Small cell osteosarcoma Круглоклеточная остеосаркома / Round-cell osteosarcoma	9185/3
Центральная остеосаркома / Central osteosarcoma Обычная центральная остеосаркома / Common central osteosarcoma Медуллярная остеосаркома / Medullary osteosarcoma	9186/3
Внутрикостная высокодифференцированная остеосаркома / Intraosseous highly differentiated osteosarcoma Внутрикостная остеосаркома низкой степени злокачественности / Low grade intraosseous osteosarcoma	9187/3
Паростальная остеосаркома / Parosteal osteosarcoma Юкстакортикальная остеосаркома / Juxtacortical osteosarcoma	9192/3
Периостальная остеосаркома / Periosteal osteosarcoma	9193/3
Поверхностная остеосаркома высокой степени злокачественности / Superficial osteosarcoma of high malignancy	9194/3
Интракортикальная остеосаркома / Intracortical osteosarcoma	9195/3

Note: NOS — not otherwise specified.
Примечание: БДУ — без дополнительных уточнений.

mTOR SIGNALING PATHWAY

mTOR (Mechanistic, formerly mammalian, target of rapamycin), as the name suggests, is the direct target of rapamycin action. Rapamycin (sirolimus) is a substance first obtained from the culture of bacteria of the *Streptomyces hygroscopicus* species found on Easter Island (Rapa Nui). Rapamycin, by inhibiting the mTOR signaling pathway, was found to exhibit unique anti-fungal, immunosuppressive and antitumor properties [26–28].

mTOR is a serine / threonine protein kinase of the PI3K-related kinase family that forms the catalytic subunit of two different protein complexes: mTORC1 and mTORC2 [26, 28].

It has been found that mTORC1 plays a central role in controlling the balance between anabolism and catabolism in response to environmental conditions, regulates the relationship between nutrition and cell growth, and mTORC2 in turn is responsible for cell survival and tissue proliferation. Thus, it is obvious that mTOR regulates the processes of cell and whole organism life activity at the deepest level [26, 29, 30].

Researchers have suggested that hyperactivation of this signaling pathway may lead to the development of a large number of aging-associated diseases, including stimulation of carcinogenesis. This hypothesis was confirmed experimentally [26, 31, 32].

Let us elaborate on the relationship between mTOR hyperactivation and the pathogenesis of osteoarcoma.

Fig. 4. Subtypes of osteosarcomas (according to Musaev E.R.)

Рис. 4. Подтипы остеосарком (по Мусаеву Э.Р.)

ROLE OF mTOR SIGNALING PATHWAY IN THE PATHOGENESIS OF OSTEOSARCOMA

It has been found that mTORC1 activates the enzyme S6K (ribosomal protein kinase), which in turn phosphorylates and activates several substrates that promote mRNA translation, including eIF4B (a positive regulator of 5'cap complex binding). S6K also enhances the translation efficiency of spliced mRNA (EJK) through its interaction with SKAR (a component of exon-junction complexes) [33]. In addition, S6K suppresses the action of programmed cell death protein (PDCD4 — eIF4B inhibitor) [34]. On top of that, mTORC1 itself inhibits the action of the 4EBP complex (eukaryotic translation initiation factor eIF4E binding protein) [35]. All of the above induces protein synthesis and tumor cell growth.

In addition, mTORC1 suppresses the action of MGMT methyltransferase and NDRG1 regulatory protein, which promotes the accumulation of errors in the genome and also contributes to carcinogenesis [36].

Autophagy is a physiological process by which cytoplasmic material is delivered to the lysosome to provide energy and nutrients to the cell. It is a strategic cell survival mechanism that allows cells to reuse energy and nutrients under extreme conditions. In addition, the process of autophagy recycles damaged organelles and proteins. This enables the cells of the whole organism in general and bone tissue cells in particular to cope with oxidative stress, which has an anticarcinogenic effect [37, 38].

mTORC1 blocks this process. It suppresses the action of such important activators of autophagy as ULK1 (kinase) and ATG14L complex [37], as well as the transcription factor of lysosomal hydrolases and membrane proteins (TFEB) [38].

Thus, drugs inhibiting mTORC1 in this respect have a complex dose-dependent effect. Under physiological conditions, autophagy activation prevents carcinogenesis, but it can also improve the survival of osteosarcoma cells under conditions of nutrient deficiency and chemotherapy with other cytostatics. This phenomenon can be leveled by combining rapalogs with autophagy inhibitors, which will be mentioned later [28, 30, 31].

At the same time, hyperactivated mTORC2 complex promotes carcinogenesis. It activates SGK (kinase), a FoxO1/3a substrate inhibitor, which prevents apoptosis of osteosarcoma cells [39–41]. Along with this, mTORC2 activates Akt (a key effector of insulin signaling), which further inhibits FoxO1/3a substrate and also stimulates proliferation [39, 41, 42]. In addition, mTORC2 promotes the secretion of interleukin-1 (IL-1), which activates angiogenesis in growing tumors [39, 41, 43]. Hyperactivation of mTOR may also indirectly contribute to osteosarcoma metastasis [39, 41].

It should be noted that mTORC1 and mTORC2 are in a complex inter-regulatory relationship. Thus, mTORC1 phosphorylates S6K, which suppresses mTORC2 activity, while mTORC2 in turn stimulates mTORC1 via the Akt-TSC-Rheb pathway [28, 30].

All the above-mentioned interrelationships are clearly represented in the summarizing scheme (Fig. 5).

DRUGS AFFECTING THE mTOR SIGNALING PATHWAY IN THE THERAPY OF OSTEOSARCOMA

The use of rapamycin and its derivatives, such as everolimus and temsirolimus, for the treatment of tumors, including osteosarcoma, has been proposed for quite some time. However, despite good in vitro results, no significant improvement in patient survival has been achieved. As mentioned above, this is largely due to the fact that rapalogs, by activating autophagy in tumor cells, increase their survival under extreme conditions. In addition, this group of drugs has been

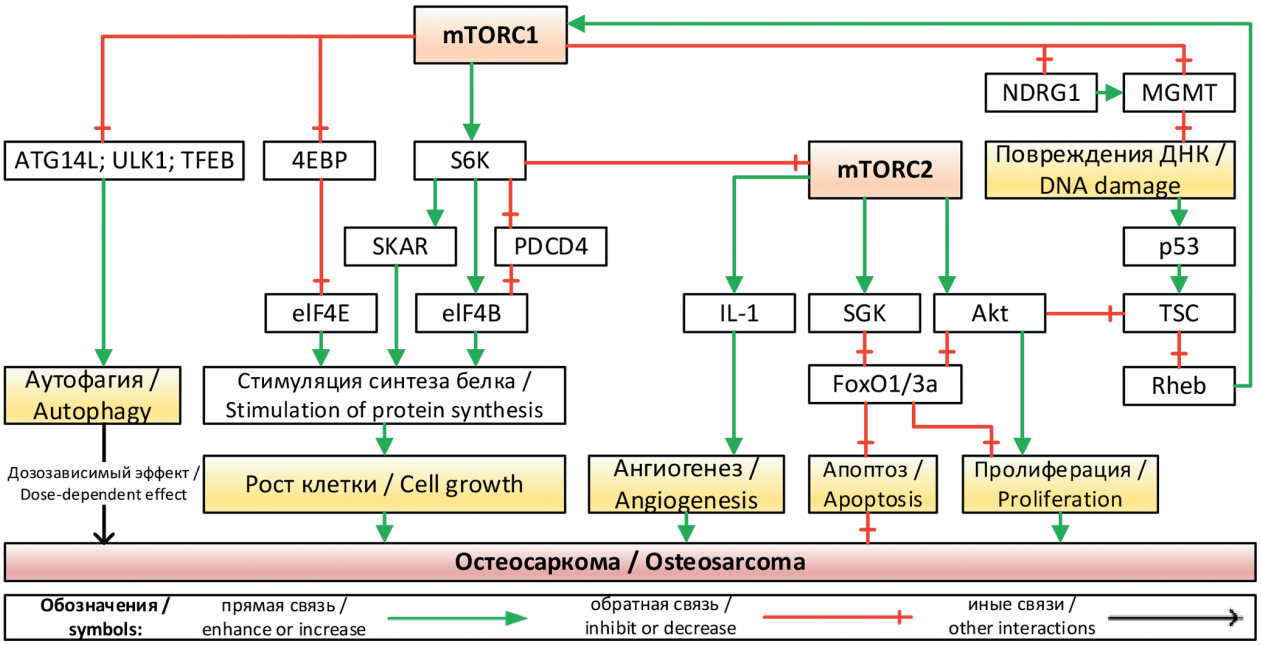

Fig. 5 **The role of hyperactivation of the mTOR signaling pathway in the development of osteosarcoma: mTORC1 — mammalian target of rapamycin complex 1; mTORC2 — mammalian target of rapamycin complex 2; S6K — ribosomal S6 Kinase; 4EBP — eukaryotic translation initiation factor 4E binding protein; SKAR — a component of exon-junction complexes; PDCD4 — programmed cell death protein 4; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; ATG14L — autophagy related 14; ULK1 — unc-51 like autophagy activating kinase 1; TFEB — transcription factor EB; MGMT — O6-alkylguanine DNA alkyltransferase; NDRG1 — N-myc downstream regulated 1; p53 — transformation-related protein 53; TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; IL-1 — interleukin-1; SGK — serum/glucocorticoid regulated kinase; Akt — RAC-alpha serine/threonine-protein kinase; FoxO1/3a — forkhead box protein O1/3a**

Рис. 5. **Роль гиперактивации сигнального пути mTOR в процессе развития остеосаркомы: mTORC1 — мишень рапамицина млекопитающих комплекс 1; mTORC2 — мишень рапамицина млекопитающих комплекс 2; S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; SKAR — компонент экзон-переходных комплексов; PDCD4 — белок программируемой клеточной гибели 4; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; ATG14L — связанный с аутофагией комплекс 14; ULK1 — unc-51-подобная киназа, активирующая аутофагию 1; TFEB — фактор транскрипции EB; MGMT — O6-алкилгуаниновая ДНК-алкилтрансфераза; NDRG1 — N-myc, регулируемый ниже по течению 1; p53 — связанный с трансформацией белок 53; TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; IL-1 — интерлейкин-1; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; Akt — RAC-альфа серин/треонин-протеинкиназа; FoxO1/3a — раздвоенный блок O1/3a**

shown to inhibit the mTORC1 complex but not mTORC2, which also limits their therapeutic effect [28, 31, 39, 41].

Therefore, new drugs inhibiting both complexes have been developed. These include catalytic inhibitors of mTOR, such as MLN0128 [44] and PP242 [45], an ATP-competitive inhibitor of mTOR kinase; microRNAs (miR-101 [46] and miR-223 [47]), a promising class of drugs that affect the genetic apparatus of the cell and inhibit mTOR protein expression, and several others. Activity against both complexes was also shown for oleanolic acid [48].

These drugs, in turn, were proposed to be combined with autophagy inhibitors such as spautin-1. This combination was able to significantly enhance apoptosis of osteosarcoma cells [49].

In addition, metformin, which activates TSC, the most important inhibitor of mTORC1, has been proposed for the treatment and prevention of malignant neoplasms, including osteosarcoma [50]. The drug is economically advantageous; moreover, its ability to overcome the negative effect of high glucose concentration on osteogenesis is of great interest [51].

The points of action of the described drugs are presented in the summarizing scheme (Fig. 6).

It should be noted that most of these drugs are an addition to classical chemotherapy. They are proposed to be combined, in particular, with doxorubicin, cisplatin, adriamycin, high doses of methotrexate with leucovorin, etc. [39, 41]

Such combinations as temsirolimus and cisplatin; temsirolimus and bevacizumab; mTOR catalytic inhibitors (PP242 or microRNA) in combination with cisplatin; cucurbitacin B (ERK, Akt and mTOR inhibitor) in combination with low doses of methotrexate have already demonstrated their efficacy in osteosarcoma models [39, 41].

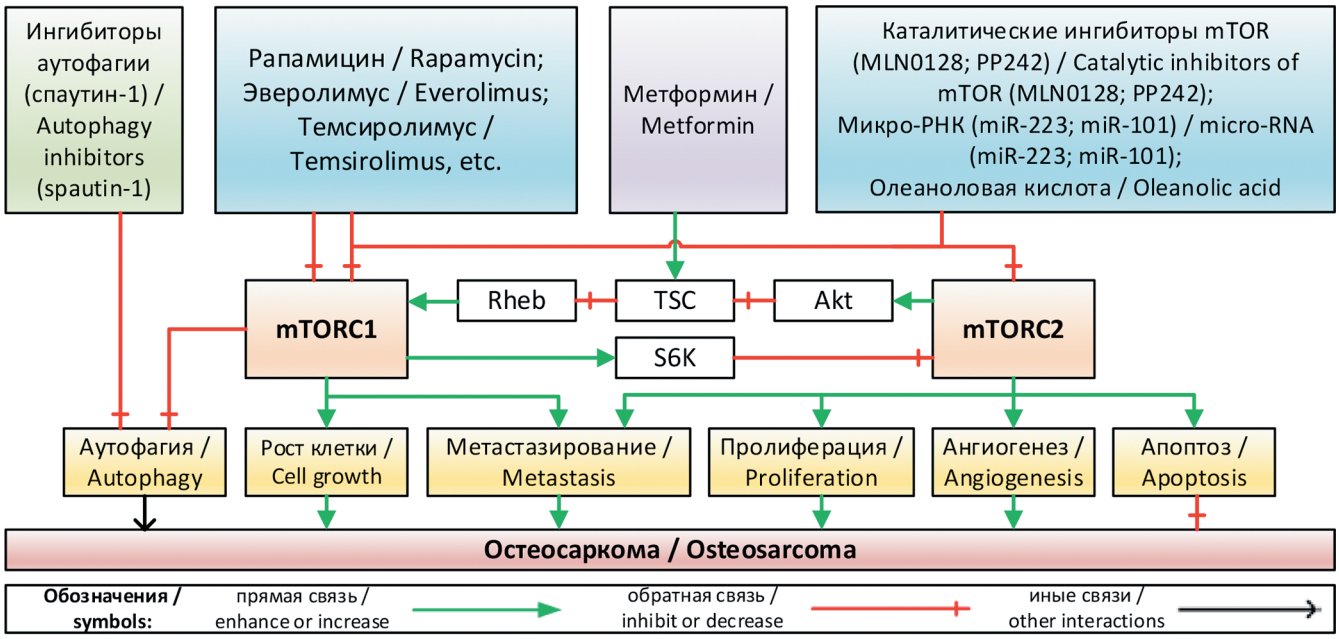

Fig. 6. **Drugs affecting the mTOR signaling pathway in the treatment of osteosarcoma: mTORC1 — mammalian target of rapamycin complex 1; mTORC2 — mammalian target of rapamycin complex 2; Rheb — Ras homolog enriched in brain; TSC — tuberous sclerosis complex; Akt — RAC-alpha serine/threonine-protein kinase; S6K — ribosomal S6 Kinase; PP242 — selective mTORC2 inhibitor**

Рис. 6. **Препараты, влияющие на сигнальный путь mTOR, в терапии остеосаркомы: mTORC1 — мишень рапамицина млекопитающих комплекс 1; mTORC2 — мишень рапамицина млекопитающих комплекс 2; Rheb — гомолог Ras, обогащенный в мозге; TSC — комплекс туберозного склероза; Akt — RAC-альфа серин/треонин-протеинкиназа; S6K — рибосомальная S6-киназа; PP242 – селективный ингибитор mTORC2**

CONCLUSION

Thus, despite the significant development of surgical and conservative treatment methods, osteosarcoma, and in particular osteosarcoma of the spine, remains a threatening nosology with an unfavorable prognosis. Studies of the mTOR signaling pathway not only shed light on aspects of the pathogenesis of this disease, but also contribute to the development of completely new therapeutic regimens. It is possible that in the near future any of the drug combinations described above will be approved for the treatment of patients with osteosarcoma.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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