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Targeted Therapy during Treatment of Bone Cancer

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Targeted medications behave differently than standard chemotherapeutic (chemotherapeutic) medications and tend to show different side effects. Targeted drugs are especially important in the treatment of bone cancer for which chemotherapy has been of little help chordoma [1]. Targeted drugs used to treat certain types of osteosarcoma are known as kinase inhibitors. Kinases are intracellular (or surface) proteins that normally transmit signals. Blocking certain kinases can stop or slow the growth of some tumors. These medicines are most commonly used to treat chordoma that has spread or returned after treatment. Some of these medicines can also be used to treat advanced chondrosarcoma. Examples of kinase inhibitors are imatinib (Gleevec), dasatinib (Sprycel), sunitinib (Sutent), ellotinib (Tarceva), lapatinib (Tykerb), sorafenib (Nexavar), regorafenib (Stivarga), pazopanib (Votrient). It is given and used in the form of pills. However, the side effects of these medications vary depending on the medication used and include diarrhea, nausea, muscle aches, and malaise. Some of these medicines cause an itchy rash and water buildup around the eyes, feet, or abdomen.

Effect of drugs on bone cells

Denosumab (Xgeva) is a drug known as a RANKL inhibitor. The RANKL protein usually tells cells called osteoclasts to destroy bone. Denosumab can block this by binding to RANKL. This drug can be used to treat giant cell tumors of bone that have relapsed after surgery or cannot be surgically removed. This drug is injected subcutaneously (subq or SQ). It often takes several months for the tumor to shrink. Denosumab is a fully humanized IgG2 monoclonal antibody against RANKL. RANKL is a member of the Tumor Necrosis Factor (TNF) superfamily and is expressed on the surface of osteoblasts. Soluble RANKL is released into the bone microenvironment, where it binds to and activates the immature osteoclast receptor RANK and functions as an important component of osteoclast differentiation and activation. The expression level of RANKL is based on various hormones and cytokines such as macrophage colony stimulating factor, TNF, prostaglandin (PGE2, etc.), steroids, parathyroid hormone (PTH), PTH-related protein (PTHrP), and interleukin (IL). Affected 1, 6, 8 and 11 [2]. In bone metastases, these and other factors such as macrophage inflammatory protein (MIP) 1α are also secreted by tumor cells, increasing osteoclast activity. In addition, tumor cells secrete factors such as Dickkopf1 (DKK1) and activin A, which inhibit osteoblast differentiation. Bone resorption, on the other hand, releases growth factors (transforming growth factor β, insulin-like growth factor, fibroblast growth factor, platelet growth factor) from the bone matrix and stimulates tumor growth [3]. The monoclonal antibody denosumab binds to RANKL and prevents bone resorption by inhibiting both mature osteoclast function and osteoclast differentiation, thereby breaking this vicious cycle of bone destruction [4]. Most side effects are mild and include body aches, malaise, diarrhea, and nausea. A rare but very serious side effect of denosumab is a jawbone injury called jawbone necrosis (ONJ). This can lead to tooth loss and / or infection of the jawbone. ONJ can be caused by dental treatment while taking the medicine. Good oral hygiene, such as dental floss, brushing, and denture confirmation, and regular dental examinations can prevent this. Most doctors recommend that patients have a dental examination and treatment of dental and jaw problems before starting this dosing.

Bisphosphonates

BP is a naturally occurring synthetic analog of pyrophosphate and is chronologically classified into three generations based on its activity and chemical structure (1st generation clodronic acid, 2nd generation alendronate, 3rd generation zoledronic acid). BP forms a bond with the crystal surface and suppresses the dissolution of hydroxyapatite crystals in bone tissue. In addition to this physicochemical stabilization of bone structure, BP is internalized by osteoclast endocytosis and is metabolically integrated into the non-hydrolyzable analog of adenosine triphosphate (ATP). These metabolites accumulate in osteoclasts, inhibit their absorption capacity, and induce apoptosis by inhibiting ATP-dependent enzymes [5]. Nitrogen BP (NBP), 2nd and 3rd generation BPs also inhibit farnesyl diphosphate (FPP) synthase, a key enzyme in the mevalonate pathway. This ability makes zoledronic acid (ZA) up to 10,000 times more potent than first-generation BP clodronic acid in some preclinical experiments. Loss of FPP synthesis and its downstream metabolites interferes with post-translational modification of small GTPases such as Ras, Rab, Rho, and Rac. These important signaling proteins regulate various cellular processes that are important for osteoclast function. In addition, disruption of the mevalonate pathway causes the accumulation of isopentenyl pyrophosphate (IPP) in osteoclasts, which is converted to a cytotoxic ATP analog called ApppI.

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