ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Review of Malignant Bone Tumors.

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ABSTRACT

Bone tumors can either be benign (non-cancerous) or malignant (cancerous). The latter are more prevalent than the former. The two types of tumor manage to grow and put a pressure on a healthy bone tissue, get absorbed in it, and finally replace the healthy tissue by an unnatural one. Benign tumors which are not spread are seldom life-threatening. A cancer which stems from bones (primary bone cancer) does not resemble a cancer spread throughout bones from other parts of body (secondary bone cancer). Primary bone cancer is scarce. In America, about 2,500 new cases of bone cancer are diagnosed annually. Prevalently, bone cancers occur as a result of the spreading of metastatic cancers in other body organs such as breasts, lungs and prostate. The most prevalent type of bone cancer is called osteosarcoma which appears in new bone tissues which are growing. Another type of bone cancer is chondrosarcoma which arises from cartilage. Ewing's sarcoma is yet another type of bone cancer which is estimated to stem from immature neural tissues in bone marrow. Osteosarcoma and Ewing's sarcomaare often prevalent among children and adolescents, while chondrosarcoma is mostly evident in adults. Bone osteosarcoma involves knees, upper parts of arms; chondrosarcoma involves pelvic cartilage and the upper parts of ankles and shoulders; Ewing's sarcoma in turn involves immature neural tissues often in pelvic bone marrow, upper parts of ankles, ribs and arms. Pain is the most common symptom of bone cancer. Symptoms are dependent on the cancerous organ and also the size of cancer. Tumors appearing in joints or near them cause inflammation or sensitivity in the afflicted area. Moreover, bone cancer disrupts the natural movement of bones and also weakens them. Occasionally, it causes fracture in them. Among its other symptoms are fatigue, fever, loss of weight and anemia. None of these symptoms, though, are definite signs of cancer. They might occur as a result of other non-threatening circumstances. However, they need to be controlled by physicians. Different tests are used to precisely diagnose this disease and examine the form and spread of cancer. These include blood or urine tests and medical imaging methods such as simple radiography, sonography, CT scan, MRI or radionuclide scan (bone scan). In the majority of cases, diagnosing the type of bone tumor depends on extracting part of the afflicted tissue and examine it microscopically. Several methods are used to treat bone tumors. It needs to be mentioned that to treat some of these tumors especially the malignant, more than one method is used simultaneously or consecutively. The key therapeutic methods for bone tumors are radiotherapy, chemotherapy and surgery.

Keywords: malignant, bone tumour, benign,

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ISSN: 0975-8585

INTRODUCTION

Bone cancer can occur from infancy to an old age. It could paralyze an organ or even cause death. Bone cancer is also known as sarcoma and is prevalent all over the world. Other cancers in body such as breast cancer, lung cancer thyroid and kidneys can be metastatic to bones and begin to annihilate them. Bone cancer occurs when the bone-making cells face a problem [1]. Every year in the U.S. this cancer is diagnosed in the form of bone tumors in over 2,000 people. It is more prevalent among children and adolescents [2]. Its prevalence is reduced with a growth of age and is, therefore, less observed among the elderly. However, it does not imply that adults do not get afflicted. Metastatic bone cancer is more prevalent among adults. This type of cancer is spread to bone from another afflicted body organ [3].

The majority of patients suffering from bone tumors feel pain in their bone. The pain is vaguer and its intensity is so high that awakens the patient [4]. Bones can be weakened and break easily as a result of a light blow. Sometimes the tumor causes no pain and the patient only gets aware of a bump in his/her limb. Depending on their type and the afflicted organ, different tumors show to have different symptoms [5].

Bone tumors:

Tumor is defined as a massive tissue produced as a result of an abnormal and uncontrollable growth of a group of cells [6]. When this mass of tissue resides in bones, it is called a bone tumor. While the tumor grows, the bone is replaced by a tissue which is not as hard as bone and is, therefore, easily broken. This tumor can be categorized as primary and secondary types. The former afflicts the tissues and cells derived from bones and the latter is metastasized to bones [7].

Primary benign tumors are: osteoma,osteoid osteoma, osteochondroma, osteoblastoma, enchondroma, bone giant cell tumor, aneurismal bone cyst and bone fibromyalgia dysplasia [4].

Primary malignant tumors are: osteosarcoma, Ewing's chondrosarcoma, sarcoma and fibrosarcoma [2].

Secondary tumors include metastasis from breast cancer, lung cancer and prostate cancer [8].

The most prevalent primary malignant bone tumors are: Multiple Myeloma: It is the most prevalent primary malignant bone tumor. It stems from bone marrow cells. Every year, this tumor afflicts 5-7 people from among a hundred thousand populations. It is mostly common among the 50-70 year-old age group [2, 4].

Symptoms:

Initially, this disease can be void of any symptoms. However, when it grows plasma cells aggregate in bones and produces the symptoms below:

Bone pain stems from lytic lesions; fatigue is the result of anemia; fever, loss of weight, pathologic fractures and constipation are due to an increased blood calcium; kidney problems are caused by the sedimentation of light chain proteins; infections in different organs are the result of malfunctioning antibodies [4, 9].

Risk factors [10]:

- Age higher than 65 years
- Male gender
- African American race
- Family history of affliction with the disease

Some people who meet these criteria get afflicted with this disease. These circumstances could be the diverse forms of multiple myeloma:

Monoclonal Gammopathy of Undetermined Significance (MGUS):

In this disease, an unnatural protein called M exists in blood which is produced by plasma cells themselves [11].

The prevalence of multiple myeloma rises with an increase of age. It rarely afflicts people younger than 40 years of age. Due to its prevalence among the elderly those afflicted with it should be taken care of from the early stages. Backache which is one such symptom should be taken seriously among the elderly. Bone marrow transplantation can be a useful treatment which can prevent the recurrence of disease. Among the elderly, however,this is not applicable [12].

Diagnosis

Once the doctor suspects a multiple myeloma, s/he would request for urine and blood tests as well as bone marrow sampling. These can help to diagnose the disease.

A number of lab-based values which can be the sign of multiple myeloma are [12, 13]

- high load of blood calcium
- anemia
- high creatinine (kidney malfunctioning)
- high load of protein in blood along with low albumin
- proteinuria
- In case the number of cell plasma is found to be high (over 30%) in bone marrow sampling, one can be diagnosed with this disease.

Treatment

Although those afflicted with multiple myeloma carry symptoms upon diagnosis, the asymptomatic might require no treatment.

In suspicious cases it is better for the patient to have no treatment for 2 or 3 months and once the symptoms of the disease or signs of its progress are observed, the treatment should begin [1, 2].

Bone marrow transplantation is one therapy for these patients and is more often used among the young. Chemotherapy is the best therapeutic method for patients tackling with the disease symptoms, those above 70 years of age and young patients who cannot have a transplantation [14].

Whenever there is a sign of the disease recurrence, the chemotherapy would begin anew. If the disease recurrence is 6 months or longer, the mere consumption of medication is suggested. Prescribing 50 milligrams of Prednisolone every 48 hours would lengthen the plateau phase and consequently patient's life [15].

Autologous transplant: Today, stem cell transplantation has replaced bone marrow transplantsince the number of myeloma cells is lower in this transplantation type and the whole process is done faster and better. This method can be used for more patients since there is no age limitation and the lack of proper donator [6]. But there are yet two issues to be considered:

- Despite the consumption of high doses of anti-cancerous drugs, cancerous cells are still there.
- Injection of the stem cells collected and stored could contain myeloma cells or their leader cells which can contribute to the recurrence of disease.

The mortality rate of this therapeutic method is 1-2%. The majority of patients are initially treated for 3 to 4 months with the VAD protocol which is less harmful than hematopoietic cellsup until the number of cancerous cells is reduced. Then the patient is treated by G.CSF with or without cyclophosphamide. One's stem cells are collected. After an improvement due to a high dose of melphalan or other diets one is prepared for

the treatment and the stem cells are injected to him/her. The other method is that after the collection of stem cells, the patient is treated with alkylating agents so that s/he reaches the plateau phase and recovery. They would then wait for the recurrence symptoms to appear and just then a high dose of melphalan is prescribed and stem cell transplantation is carried out [6].

The transplant can be done early or late. The benefit of an early transplant is that the patient would receive fewer cytotoxic drugs. The benefit of a late-coming transplant is that the therapeutic method as well as the method of controlling the patient can be improved in future. The value of segregating and collecting leader cells with the help of CD34 antigen is that fewer cancerous cells exit in it. There is a need for further research with this regard [15, 16].

Allogenic transplant

The advantage of this type of transplant is that it contains no cancerous cells. In case there is a transplant, it has a graft versus myeloma effect. However, 90% of patients cannot use this method due to their: age, having no matched siblings in terms of HLA, heart, kidney or lung failure. The disadvantage of this therapeutic method is its 25% mortality rate within its first 3 months which also reaches 40% in the following months [17]. The majority of patients who experience a recurrence of the disease do not reach the plateau phase immunological method used in this therapy is the injection of donor's lymphocytes to patients who experienced are occurrence of disease [2]. As the results of an investigation showed, from among 13 patients who had a recurrence of disease, 8 of them benefited from this therapy [17].

Treatment of patients who resist to medication or those with a recurrence of the disease

Patients who are resistant or have become resistant to primary medical protocols including alkylating agents are hardly responsive to subsequent therapies. The most effective therapy for those resisting against alkylating agents is VAD protocol [17, 18].

80% of the therapeutic effect of this protocol is due to Dexamethasone. Therefore, this medicine can be used on its own to treat these patient [2, 18].

Intravenous injection of Vincristine 4 mg and doxorubicin 2 mglm among 134 patients who had not been treated before led to a 67% of improvement. Therefore, there is no need for these drugs to be constantly injected intravenously along 24 hours for 4 days. That might be problematic [19]. Prescribing intravenous injection of methylprednisolone 2g, 3 times a week is useful for patients with pancytopenia or those with a recurrence of the disease [20]. Its negative side effects are fewer than dexamethasone [7].

A combination of Doxorubicin-B-CNU and Vincristine on the first day, and prednisolone for 5 days every 3 to 4 weeks managed to treat one-third of patients resistant to therapy [19]. Thalidomide was found to be effective in 32% of 84 patients who had already gone through chemotherapy and their disease was on progress. After a one-year follow-up 22% of these patients showed to have no symptoms and 58% survived [7, 19].

Osteosarcoma: It is a malignant bone tumor of an osteoblastic origin which is the most prevalent tumor among the young. Its prevalence rate is 1-3 cases per a million people a year. The mere osteosarcoma comprises 20% of malignant bone tumors [3, 19, 20]. It seems to arise from the primary constituent bone cells. Production of a malignant bone mass is its evident histologic symptom. The basics of its treatment include: biopsy, surgery to remove the tumor and chemo-therapy to kill the microscopic metastases(20). Although secondary osteosarcoma rarely occurs among the young, it can be observed among those who experienced radiotherapy as a secondary type. This type of osteosarcoma often afflicts uncommon limbs with a few-year delay after the radiotherapy. Secondary osteosarcoma could also occur among the elderly with a Paget's disease [20, 21].

Symptoms

The most common symptoms of osteosarcoma are pain and inflammation in one's arm or leg which is usually accompanied by a tumor(21, 22). For some patients the pains are sharper at night or during physical

exercises. This cancer occurs more in the bones surrounding knees, but is also observed in other bones [22]. In some cases, the tumor can be spread to lungs or other bones. It can also metastasize to other limbs. Pain gets sharper once the bone is pressed. Swelling and even redness can be observed in some parts of body. Laminitis and motion limitation in joints can be other symptoms of the tumor. If the tumor grows further, it can even break the bone [21, 23].

These cancers often occur among children and young adults especially those who go through radiotherapy or chemotherapy for other diseases [22, 23]. Adults suffering from Paget's disease are prone to a high risk of osteosarcoma [21]. A few of bone cancers are related to hereditary factors. As an instance, children afflicted with congenital retinoblastoma are more prone to osteosarcoma [23].

Diagnosis of osteosarcoma tumor

The tumor can be visible in a simple radiography image. An orthopedist may use other imaging techniques such as radioisotope scan, CT scan and MRI in order to help the diagnosis and investigate the extent to which the tumor has been spread [21, 24]. An absolute diagnosis of this disease is only possible through extraction of part of the tumor via biopsy. The pathologist would examine the tissue with great care using a microscope and determine its type [24].

This tumor is observed in the radiography as a lesion with a sunray appearance and a periosteal reaction known as Colman's triangle [21, 24].

Treatment of an osteosarcoma tumor

Primary therapeutic methods for osteosarcoma are

Chemotherapy

It is usually prescribed in advance to a surgery so as to reduce the size of the tumor and let the surgery be done more easily and conveniently [21]. Chemotherapy would continue after the surgery as well [25].

Radiotherapy

Osteosarcomadoes not generally respond positively to radiotherapy. However, for patients who have just had a surgery, it could be used in order to get rid of the remaining parts of the tumor [25]. In case the bone is broken due to osteosarcoma, the cancerous cells might be spread to the surrounding tissues. To fight against these cells, radiography is used too [26].

Surgery

During surgery, the cancerous tissue along with part of the healthy bone are extracted [25, 26]. The hollow space is either filled with bone prosthesis or bone transplantation to replace the bone gone. Occasionally the tumor is spread so widely that has already afflicted many limbs and has injured tissues and nerves. Therefore, the best way would be an amputation of the organ [26].

Ewing's sarcoma

It is a type of primary malignant bone tumor in which bone marrow cells get modified in their nucleus and cellular chromosome and they become cancerous [27]. As compared to osteosarcoma, it can reveal itself in younger age groups. Contrary to other types of bone tumors, it can come along a series of symptoms such as fever, loss of appetite and weight [2, 27]. Similar to other bone tumors, its most significant primary symptom is pain which would begin months prior to the diagnosis. The most commonly afflicted organs are the diaphysis of thigh and ankle bones(28). Ewing's sarcoma responds positively to such therapies as chemotherapy and radiotherapy [27, 29]. Its therapeutic protocol is comprised of: a chemotherapy phase upon diagnosis followed by a surgery to remove the tumor and finally a continuation of chemotherapy after the

surgery. In case the tumor cannot be removed completely, radiotherapy can be later used in order to control its growth [27].

Ewing's sarcoma symptoms

Pain is its most common symptom. The area afflicted with the tumor is swollen and gets painful if touched. In case the tumor is in the lower body limb, it could result in laminitis [29]. Fever is sometimes among the symptoms. In some cases, due to severe weakness, the bone might be broken. Ewing's sarcoma is often mistaken for lesions and pains caused during physical exercises [2, 30]. That is due to the fact that its symptoms are similar to injuries children and teenagers get while playing sports. Pain in the afflicted organ along with swelling and fever are the primary symptoms of this disease [29]. At night and also during sports this pain can get more acute too [30]. A few weeks after the pain, the limb might begin to move unsteadily. If the tumor has grown in ankles, the patient soon finds it hard to walk steadily. A slight fever might also concur [28].

If the cancer is metastasized to other parts of body such as lungs or bone marrow, the symptoms show up in those organs as well [30]. In some cases, the initial symptom of the disease is a broken leg or arm occurring for no reason (or just a slight blow). That is because cancer would weaken the bone and make it vulnerable to fractures [29].

To diagnose it, the doctor would first inquire about the child's medical background. He also makes a body examination [30, 31]. Then he would request tests, simple radiography, MRI or bone scan in order to diagnose bone abnormalities. A biopsy of the tumor tissue should be done which is to be later analyzed in the lab. These are all required for a correct diagnosis. Sometimes the biopsy physician decides to extract a sample of the tumor using a long syringe [31]. Some other times, he would opt for an open biopsy during which he would take out part of the tumor [28]. All this is done in an operation room by a surgeon while the child is completely unconscious. Bone tumor sampling and its analysis by a pathologist determines its absolute diagnosis. Sometimes cancerous cells are spread to lungs, other bones or bone marrow. Therefore, bone marrow sampling and analysis as well as a radiography of the chest might help the diagnosis. Upon diagnosis, the disease of about one-third of patients is metastasized [5, 31].

In case the diagnosis of Ewing's sarcoma is confirmed, the doctor would request more radiographies to come to know about the afflicted areas. These tests help to ensure the doctor whether the vital organs including heart and lungs work properly or not and also whether they can tolerate the above-mentioned therapies or not [31].

Treatment of Ewing's sarcoma

The therapeutic procedures for this disease depend on many factors such as size and location of the tumor as well as the extent of its spread [31].

Chemotherapy

Besides the symptoms of a tumor, each patient afflicted with Ewing's sarcoma should go through a chemotherapy so that the tumor is reduced in size (before the removal of tumor via surgery or radiotherapy) and the disease progress is prevented [32]. After the removal of tumor, still chemotherapy can be used to ensure about the non-recurrence of cancerous cells [1, 5]. Before the surgery, it serves the purpose of cutting down on the size of tumor so that the surgery can be done more easily. After the surgery, it will yet be continued [32, 33]. Its usual procedure takes 6 to 9 months' time. The child should be hospitalized for a couple of days during the treatment period [34]. Every 2 to 3 weeks this should be repeated. Some children should stay longer in hospital due to such side effects as fever or infection. Chemotherapeutic drugs should be injected intravenously [32, 35].

Radiotherapy

It is truly effective in treating Ewing's sarcoma. It is done either after chemotherapy or after surgery. Radiotherapy is used when the tumor is located in an organ hard to be operated on e.g. the spinal column [35].

In case there is a need for surgery, then radiotherapy is done in advance so as to reduce the size of the tumor to be removed [33]. In case the position of the tumor is hazardous for surgery, radiotherapy is always suggested instead of surgery [34]. In radiotherapy, an X ray of high energy is projected onto the tumor so as to kill the cancerous cells or to prevent their growth[35].

The majority of children who experience radiotherapy do not need to be hospitalized. They need to visit the hospital 5 days a week for a few weeks [33, 34].

Surgery

During surgery, the cancerous tissue is removed along with part of the healthy bone around it. The hollow space is filled with a metal which replaces the bone (e.g. use of a manufactured joint if the tumor is close to the joint) [34, 36]. Bone transplantation might also be used to replace the bone gone. Sometimes the growth of the tumor is so fast that it is spread to many organs and severely injures many veins and nerves. In these cases the best way might be a limb amputation[36].

Chondrosarcoma

It is considered as the most prevalent type of primary malignant tumor in chest walls. About 15-20% of all skeletal chondrosarcoma involve ribs or sternum bone [37]. Most of these tumors occur among 20-40 year old patients [37, 38]. The most common organ afflicted with this tumor is the area joining ribs and the cartilage. However, this tumor might be observed in every part of ribs, topical involvement of pleura, adjacent ribs, muscle, diaphragm, and other soft tissues [39]. However, pain is a rare symptom and the majority of patients do only complain about the tumor [38]. In the radiography image of chest, the bone cortex's destruction is visible which is often accompanied by a dissolved point calcification. The edge of the tumor is not clear either [37, 39]. The treatment includes the radical and extensive removal of lesion. Topical lymph nodes get also gradually engaged. A 5-year survival which is dependent on the (in)adequacy of the removed area in surgery is variable to a 10-30% degree [38, 39].

CONCLUSION

Since infancy to an old age, bone cancer can occur and lead to a paralyzed organ or mortality. Bone cancer is also known as sarcoma and is highly prevalent in the world(40). This tumor can be categorized as primary tumors which occur in tissues and cells derived from bones and secondary tumors which are metastasized to bones [4, 41].

Primary benign tumors include: osteoma, osteoid osteoma, osteochondroma, osteoblastoma, enchondroma, bone giant cell tumor, bone aneurismal bone cyst and bone fibromyalgia dysplasia[40].

Primary malignant tumors include: osteosarcoma, chondrosarcoma, Ewing's sarcoma and fibrosarcoma. Secondary tumors are: metastasis from breast cancer, lung cancer and prostate cancer [40, 41].

Pain is the most common symptom of bone cancer. Symptoms are dependent on the size and location of the cancer [41]. Tumors which occur at joints or their surrounding areas cause inflammation and sensitivity in those areas. Moreover, bone cancer can disrupt bone natural movements and can weaken them. Occasionally it causes fractures too [7, 41].

Other symptoms include fatigue, fever, loss of weight and anemia. None of these symptoms are absolute signs of cancer. They might occur as a result of other non-hazardous conditions and they need to be controlled by the doctor [42].

The orthopedist needs to talk to patient about his problems and gather comprehensive information. He also needs to examine the patient and request different tests such as blood, urine as well as imaging methods including simple radiography, sonography, CT scan, MRI and bone scan (radioisotope scan)[42]. These are all used for a precise diagnosis and examination of the extent of tumor growth and involvement of other organs [7]. In most cases, the specifying tumor type requires an extraction of part of the tissue and a

microscopic examination. The surgeon might need to acquire a sample of the tumor tissue via FNA or excisional biopsy [4, 42].

Some benign tumors need no special treatment. They cause no serious problem in body. Some others might heal themselves through the passage of time. Yet some others need to be treated. Diagnosis of a cancerous tumor is the responsibility of an orthopedist specialist [3]. Various methods are used to treat bone tumors. It is noteworthy that in order to treat some tumors especially the malignant, more than one therapeutic method is used simultaneously [43]. The key methods used to treat bone tumors are:

Radiotherapy

This method is often used to treat malignant bone tumors. Projecting Gama ray onto the cancerous tissue is one effective way to remove these cells. Projecting this ray produces a number of molecules in body called free radicals that cause damage to the DNA of cancerous cells and, therefore, kill them [44, 45]. This could as well happen to healthy cells [46]. But since in cancerous cells due to a fast proliferation rate DNA is produced faster than in healthy cells, theeffect of the ray on cancerous cells is higher. Radiotherapy cannot entirely annihilate cancerous cells. It can only cut down on their number. Yet, this can be enough to reduce the pain in bones [44].

Chemotherapy

This method is often used in treating malignant tumors. One key way of treating malignant tumors is chemotherapy in which some drugs are prescribed which disrupt cellular proliferation. Since cellular proliferation is faster in cancerous cells than in healthy and natural body cells, these drugs have more destructive effects on cancerous cells than the healthy [45]. This method is commonly used in cases in which bone cancerous cells have metastasized. That is, they have spread to different parts of body and some of these parts are so small and disperse that their entire removal through chemotherapy is made impossible [47]. In the majority of cases, malignant bone tumors require a surgery. Radiotherapy and chemotherapy can help the surgery by reducing the size of the tumor, or after the surgery by removing the remaining cancerous cells in body. Sometimes, hormones are used to treat some tumors [46].

Surgery

This method is used in treating almost all benign tumors and a great many of malignant bone tumors. Benign tumors are mostly in the form of a tissue inside the bone. In the surgical procedure, the orthopedist often removes tumor tissue contents out of the bone [47]. Therefore, a hole is created inside the bone which is entirely carved out. Then the hollow space is filled by bone transplantation [45].

For malignant tumors the process is a little different. These tumors can gradually weaken the bone and this condition can grow so far that the bone easily breaks due to a light blow. Such fractures are either never or hardly fused. This is done through a surgery and inserting metals in the bone [46].

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