CURRENT APPROACHES IN THE TREATMENT OF OSTEOSARCOMAS

Akhilesh Mishra1, Gayatri Dewangan2*, Ramdas Singh3, Amartya De4, Jui Chakraborty5 and T.K. Mandal1

1Department of Pharmacology and Toxicology, West Bengal University of Animal and Fishery Sciences, Mohanpur campus, Nadia-741235, West Bengal, India.
2Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Mhow (M.P.), India.
3Department of Veterinary Pharmacology & Toxicology, College of Veterinary Sciences & Animal Husbandry, Agartala-799008, India.
4Department of Pharmacology, B.C.D.A. College of Pharmacy, Barasat (W.B.), India.
5Bio-ceramic and Coating Division, CGCRI, Kolkata-32, India.

ABSTRACT
Osteosarcoma is the most common primary tumor of bone, yet its absolute incidence among malignant tumors is low. Within its strict histologic definition, osteosarcoma comprises a family of lesions with considerable diversity in histologic features and grade. In most cases, typical radiographic features clearly illustrate the aggressive bone forming nature of the lesion. The successful treatment of patients with osteosarcoma requires close co-operation within an experienced multidisciplinary team including pediatric or medical oncologists, surgeons, physicians, pathologist and radiologists. Therapy must include complete surgical removal of all detectable tumor sites as well as multi-agent chemotherapy. Novel approaches are needed in order to improve their prognosis and developing to new targeted drug delivery techniques for less toxicity to the host. In this article we discuss clinical presentation, diagnosis, different types of treatment, health promotion and physico-chemical care for patients with osteosarcoma.

Keywords: Chemotherapy, osteosarcoma, methotrexate, radiotherapy, targeted drug delivery.

INTRODUCTION
Osteosarcoma is a bone tumor that most often affects children and young adult. It is the sixth leading cancer in children above 15 years of age. Osteosarcoma has been reported to occur in all bones of the body. It has an affinity with the metaphyseal portions of the long bones. In
the group of axial locations of osteosarcoma, pelvic osteosarcomas account for approximately 7-9% of all osteosarcomas.\textsuperscript{[1]} Researchers are learning more about the causes of osteosarcoma. It is hoped that knowing more about the DNA changes that cause this cancer will eventually result in specific treatments to correct these changes. Tests of gene changes called gene expression profiling might help predict the behavior of each tumor such as how they will respond to certain types of chemotherapy. These are still being tested in clinical trials. Osteosarcoma (OS) is the most frequent primary malignant bone tumour, mainly affecting children in the first and second decade of life.\textsuperscript{[2]} The percentage of osteosarcoma among children (aged 0-14 years) and adolescents (aged 15-19 years) diagnosed with malignant bone tumours in Europe during 1978-1997 were 51% and 55% respectively.\textsuperscript{[3]} This tumor had their highest incidence in late childhood or early adolescence.\textsuperscript{[3]} It is most commonly arises from the metaphysis of the bone. It is extremely rare in children before age of 5 years. It is slightly more common in males than in females.\textsuperscript{[4]} The incidence in black children is higher than that in whites.\textsuperscript{[5]} Although significant treatment progress in osteosarcoma has been made over the past two decades, the overall survival benefit is considerably less dramatic than widely assumed. Osteosarcoma appears in distinct clinical forms having different degree of malignancy and prognosis.\textsuperscript{[6,7,8]} Several other sub groups have a much poorer prognosis. Many of these patients may die without detectable metastatic disease due to failure to obtain local tumor control.\textsuperscript{[9]} Treatment may consist of surgery, chemotherapy or both. Multi-modality treatment, which is treatment using two or more techniques, is increasingly recognized as an important approach for increasing a prolonging survival. In some cases, participation in a clinical trial utilizing new innovative therapies such as methotrexate with nanocarrier materials may provide the most promising treatment. Circumstances unique to each patient’s situation may influence how these several treatment principles are applied and whether the patient decides to receive treatment. The potential benefits of multi-modality care, participation in a clinical trial or standard treatment must be carefully balanced with the potential risks. Small cell osteosarcoma is a rare histologic variant of osteosarcoma with histologic features combining those of osteosarcoma and Ewing Sarcoma.\textsuperscript{[10]} It constitutes between 1-2% of all osteosarcomas.\textsuperscript{[11]} The only radiologic features are not consistently typical for osteosarcoma because there often is very little mineralized matrix produced. For this problem, biopsy a gold method was to determine the disease. Histologically, it may be mistaken for Ewing Sarcoma/primitive neuroectodermal tumor (PNET) because its cells are small and have round, hyperchromatic nuclei with very little of the nuclear pleomorphism characteristic of conventional high grade osteosarcoma.
Several subtype of osteosarcoma can be identified:

(A) **High grade osteosarcoma**: These are the faster growing types of osteosarcoma. There are again several types of high grade osteosarcoma
1. Osteoblastic
2. Chondroblastic
3. Fibroblastic
4. Mixed
5. Small cell
6. Telangiectatic
7. High grade surface

Other high grade osteosarcoma includes:
1. Pagetoid
2. Extra skeletal
3. Post-radiation

(B) **Intermediate grade osteosarcoma**: These uncommon tumors fall in between high grade and low grade osteosarcoma such as periosteal etc.

(C) **Low grade osteosarcoma**: These are the slowest growing osteosarcoma in which includes:
1. Periosteal (Juxtacortical low grade)
2. Intramedullary or intra-oseous well differentiated low grade central

Other types include malignant bone tumors and benign bone tumors.

**Causes**
Osteosarcoma is the most common cancerous bone tumor in kids. The average age at diagnosis is 15 years. It is also more commonly seen in people over age of 60. The actual cause is not known till date. In some cases, osteosarcoma runs in families. At least one gene has been linked to an increased risk. This gene is also associated with familial retinoblastomas, a cancer of the eye that occurs in children.

Osteosarcoma tends to occur in the bones of the:
- Shin (near the knee)
- Thigh (near the knee)
- Upper arm (near the shoulder)
However, this cancer occurs most commonly in larger bones and in the area of bone with the fastest growth rate. Osteosarcoma can occur in any bone.

**Symptoms**
1. Bone pain
2. Bone fracture (may occur often what seems like a routine movement)
3. Limitation of motion
4. Limping (if tumor in the leg)
5. Pain when lifting (if the tumor is in the arm)
6. Tenderness, Swelling or redness at the site of the tumor

**Pathophysiology**
Osteosarcoma has a predilection for developing in rapidly growing bone. A number of studies have established a correlation between the rapid bone growth experienced during puberty and osteosarcoma development.\(^{12,13}\) Fifty-six patient of all osteosarcomas present around the knee.\(^{14}\) The epiphyseal growth plates of the distal femur and proximal tibia are responsible for a great deal of the increase in height that occurs during puberty. Additionally, the peak age of osteosarcoma development is slightly earlier for females, an observation that may be explained by the relatively earlier growth spurt experienced by girls.\(^{15}\) There is a male:female ratio of 1.5:1 for osteosarcoma and patients affected by the disease are taller compared to the normal population of the same age group.\(^{16}\) Patients affected by Paget’s disease, a disorder characterized by both excessive bone formation and breakdown, also have a higher incidence of osteosarcoma. Physical, chemical and biological agents have been suggested as carcinogens for osteosarcoma. Among these, the role of UV and ionizing radiation is the best established. The initial pathogenic link between radiation exposure and osteosarcoma was noted in female radium dial workers who applied radium to watch faces to make them luminescent.\(^{17}\) The chemical agents linked to osteosarcoma formation include 4-nitroquinoline 1-oxide, chromium salts, beryllium oxide, zinc beryllium silicate, asbestos and aniline dyes.

A recent study of pre-therapeutic biopsy specimens has identified amplifications and chromosomes 6p21, 8q24, and 12q14 as well as less of heterozogosity of 10q21.1 as being among the most common genomic alterations in osteosarcoma. Furthermore, it was concluded that patients carrying these alleles had a poorer prognosis.\(^{18}\) Numerical chromosomal abnormalities associated with osteosarcoma include loss of chromosomes 9, 10,
13 and 17 as well as gain of chromosome 1.\textsuperscript{[19]} The P53 gene is mutated in 50\% of all careers and 22\% of osteosarcomas.\textsuperscript{[19]} DNA damage results in phosphorylation of P53, which is constitutively inhibited by Mdm2. phosphorylation allows P53 dissociation from Mdm2. P53 exerts its tumor-suppressor effects via the activation of proapo P21. The latter binds and inactivates G1/S-cdk and S-cdk complexes causing arrest of the cell cycle in G1.\textsuperscript{[20]}

**Diagnosis**
Examinations and tests include:
- Biopsy (at time of surgery for diagnosis)
- Blood test (ALP and LDH)
- Bone scan to see if the cancer has spread to other bones
- CT scan of the chest to see if the cancer has spread to the lungs
- MRI scan
- PET scan
- X-ray

The route of osteosarcoma diagnosis usually begins with an X-ray, continues with a combination of scans (CT, PET, MRI and bone scan) and ends with a surgical biopsy. A characteristic often seen in X-ray in the ‘Codman’s Triangle’ which is basically a subperiosteal lesion formed when the periosteum is raised due to tumor. Films are suggestive, but bone biopsy is the only definitive method to determine whether tumor is malignant or benign.

**Treatment of osteosarcomas**
Osteosarcoma is very rare; they are usually treated at specialist hospitals by a team of doctors and other health professionals. Most people with an osteosarcoma will need to have a combination of different treatments. The treatments that may be used are surgery, chemotherapy and radiation therapy.

(i) **Surgical management of osteosarcoma**
Amputation is the most commonly used surgical treatment for osteosarcoma. Forelimb tumors are best removed by forequarter amputation (entire limb including the scapula) and hind limb tumors are best removed by coxofemoral disarticulation. Proximal femoral and pelvic osteosarcoma require a hemipelvectomy. Numerous techniques for limb salvage includes allograft and endoprosthesis limb salvage for distal radial osteosarcoma, bone
transport osteogenesis limb salvage for distal radial osteosarcoma and allograft limb salvage in combination with total hip replacement for proximal femoral osteosarcoma. Survival times for limb salvage techniques are the same as amputation and approximately 3-4 months without adjuvant chemotherapy. Limb salvage resection has recently become more popular than when it was first developed and it is often chosen by patients who have osteosarcomas.\textsuperscript{[21,22]}

(ii) Chemotherapy for osteosarcomas

Neoadjuvant (pre-operative) chemotherapy was introduced in 1978.\textsuperscript{[23]} The purposes of neoadjuvant chemotherapy are the destruction of primary tumor cells and the eradication of micrometastasis. Methotrexate and doxorubicin have been applied successfully as chemotherapy drugs for the treatment of osteosarcomas.\textsuperscript{[24,25,26,27]} In the course of a study into osteosarcoma chemotherapy, vincristine, bleomycin and dactinomycin have all been proven to be ineffective.\textsuperscript{[23]} Subsequently, the addition of cisplatin and ifosfamide to doxorubicin and methotrexate has been able to improve clinical results significantly. The current standard protocol of a three drug combination chemotherapy regimen using cisplatin, doxorubicin and high dose of methotrexate provides about 70% long term disease free survival for osteosarcoma patients without tumor necrosis in excess of \((\geq) 90\%\) are classified as good responders to chemotherapy, whereas those whose tumor necrosis is less than \((<) 90\%\) are classified as poor responders.

(iii) Radiation therapy

People who were treated with radiation therapy for another cancer might have a higher risk of later developing osteosarcoma in the area that was treated. Being treated at a younger age and being treated with higher doses of radiation both increase the risk of developing osteosarcoma. It is not clear if imaging test that use radiation such as X-ray, CT scan and bone scan; raise the risk of developing osteosarcoma. The amount of radiation used for these tests is many times lower than that used for radiation therapy. If there is any increased risk it is likely to be very small, but physicians try to limit in children whenever possible, just in case. Osteosarcoma is one of the most common post-irradiation sarcomas that develop either in bone or soft tissue after radiation.\textsuperscript{[28,29]} While, post-irradiation osteosarcoma in bone and soft tissue after high-dose intra-operative radiation therapy has been reported in several experimental models.\textsuperscript{[30,31]} In very high dose irradiation, tumours cells in the radiation field might die rather than survive with a potential for malignant transformation but tissue near the
edge of the irradiation field could be exposed to a lower dose of radiation scatter. In the first case, normal tissue was irradiated by both external beam radiation and by intra-operative radiation therapy in the anterior-posterior direction. It is therefore, not unusual that the tumor was induced by the radiation in the adjacent normal tissue after a long period potency. In the second case, normal tissue was out of the irradiation field during intra-operative radiation therapy, while the tumor bearing bone and adhering soft tissue were irradiated with a single dose of 50Gy. Even in this case however, the secondary tumor was potentially induced by intra-operative radiation therapy, since normal tissue near the edge of the radiation field may be exposed to low dose irradiation by beam scatter.

CONCLUSION

The current treatment chemotherapy together with surgical removal can only cure around 70% of osteosarcoma patients because of chemo-resistance; multi-drug chemotherapy has a strong positive impact on disease free survival in patients with osteosarcoma. Ongoing challenges include tailoring chemotherapy to the individual risk of relapse and the development of biologically driven treatment of strategies. Increased awareness, a high index of suspicion and appropriate early referral is crucial to enable limb salvage surgery and increase disease free survival rates. The continuing efforts in research along the targeted drug delivery therapy in osteosarcoma will hopefully improve outcomes for patients without significantly increasing toxicity.

Conflict of interest

All authors declare that they have no conflict of interest.

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