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SCRUTINY ON MANAGEMENT OF OSTEOSARCOMA

Deblina Pal [1], Arnab Chakraborty [2] and Monisha Nath [*1]

Department of Pharmaceutical Technology [*1], Department of Food Nutrition & Dietetics [2], School of Medical Sciences, Adamas University, Kolkata - 700126, West Bengal, India.

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Correspondence to Author:
Monisha Nath

Assistant Professor,
Department of Pharmaceutical Technology, School of Medical Sciences, Adamas University, Kolkata - 700126, West Bengal, India.

E-mail: monishanath007@gmail.com

ABSTRACT: Osteosarcoma begins in the long bones and occurs mainly in children and young adults but is also seen in an older population with a high mortality rate. Zinc beryllium silicate and beryllium oxide, radioactive agents like radium and some C-type viruses have a harsh impact on osteosarcoma. Genetic factors like changes in the p53 tumor suppressor gene, mutation in RECQL4 gene, WRN gene can contribute in osteosarcoma. Osteosarcoma tumor can be categorized as high grade, intermediate grade, and low grade depending on the degree and duration of tumor growth. Based on the nature of the pathogenesis and location of tumor high grade osteosarcoma can be Osteoblastic, Chondroblastic, Fibroblastic, Telangiectatic, Desmoplastic fibroma, Extraskeletal osteosarcoma; Periosteal Osteosarcoma are of intermediate grade. It is associated with some characteristic symptoms like bone pain, lump formation, and walking with difficulties leading to pathologic fractures. Osteosarcoma can be diagnosed by Biopsy, X-ray, MRI, and CT scan and from some biochemical markers like Lactate Dehydrogenase and Alkaline Phosphatase. Treatment include surgery which has wide safety margin, chemotherapy with Cisplatin and Doxorubicin after that Methotrexate, Adriamycin, Cisplatin. Preoperative chemotherapy and radiotherapy are given 2–6 cycles for 6–18 weeks. Some Phytochemicals like curcumin, genistein, and berberine positively impact osteosarcoma tissue. After completion of treatment patient should be followed up to 6 years with timely surveillance.

INTRODUCTION: Osteosarcoma is a rare type of bone cancer that begins in the osteoblast cells of the long bones and occurs mainly in children and young adults. The osteoid component of OS varies from one to another. Most of the osteoid is composed of cartilage and fibrous tissue [1]. A malignant tumor is classified as osteoblastic, chondroblastic, or fibrous if it comprises 50% of that particular cell type.

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It is reported higher in male children than in female; it is the eighth most common childhood malignancy, but mortality is higher in older individuals. Within the 14-year-old age group, osteosarcoma occurs at a rate of four cases per million people each year; within the 0-19-year-old age group, it occurs at a rate of five cases per million people each year; osteosarcoma is more likely to present as secondary cancer as a result of malignant degeneration of Paget disease, bone infarction sites in older *etc.* [2].

Established Etiology of Osteosarcoma: Pathophysiological background of osteosarcoma though unpredictable, but it may have some contributing factors, like genetics, epidemiology,

and certain viruses. A chemical compound named zinc beryllium silicate and beryllium oxide has been shown to produce atrophy in the spleen, followed by osteosarcoma in rabbit models or previously surgically removed spleen in rabbit [3]. Another radioactive chemical like Plutonium-Thorotrast injection has been shown to develop osteosarcoma practically up to 4 years of radiation [4].

Certain viruses can also contribute in osteosarcoma. These viruses are classified based on their genetic substances RNA and DNA. The C type viruses are associated with animal species' leukaemia, sarcoma, and lymphoma. In some animals, two C-type viruses are ecotropic and xenotropic; ecotropic viruses can infect same species but infect different species. FBJ virus was isolated from a spontaneously developing osteosarcoma in a mouse and it can induce osteosarcoma in newborns even if it is diluted to thousand folds[5].A genetic mutation causes leukocoria, resulting in clouded iris, poor vision, and lack of "red reflex" in the eye, a symptom associated with primary osteosarcoma Retinoblastoma. Radiation therapy changes in the p53 tumor suppressor gene result in Li-Fraumeni Syndrome, an autosomal dominant disorder. This has been found to cause osteosarcoma in children [6].

Patients with this disorder will likely develop other types of cancer very early. Rothmund-Thompson Syndrome because of a mutation in the RECQL4 gene, symptoms like early onset of poikiloderma, with characteristic rash, changes in the skin colouring, alopecia, hypogonadism, cataracts, ultimately lead to osteosarcoma [7]. Bloom Syndrome is characterized by photosensitivity, and short stature. If this syndrome is predisposed with or without other cancers, this allows better surveillance of genetic testing family members. Werner syndrome or adult progeria, is characterized by untimely aging, cataracts, osteoporosis, short stature, skin changes, and prevalence of osteosarcoma caused by faulty WRN gene [8]. Patients with Paget disease, electrical burns, alkylating agents, orthopaedic prosthetics, osteochondromatosis, enchondromatosis, as well as bone infection. Osteosarcoma is shown to be developed from a trauma-related injury, there are some cases of osteosarcoma development at the site of a bullet shot. Tobeiha *et al.*, 2021. Diamond Blackfan anaemia can also turn into osteosarcoma characterized by blood cell aplasia, congenital abnormalities in the ribosomal protein formation due to genetic mutation up to nine genes. Mostly mutation occurs in the RPS19 gene in 19q13.2 zone.

Sometimes there is a mutation in the RPL5 site along with blocking the action of the FLVCR1 causes apoptosis of erythroid progenitor and mutation in the GATA1 maturation factor. Mutated GATA1 maturation factor and activated P53 gene may ultimately causes Diamond Blackfan anaemia. Paget disease which is another suspected cause of osteosarcoma, occurs in elderly male and in more than 40 years of age. Abnormal osteoclastogenesis and osteoblastogenesis may occur due to defected and mutated growth factors. It has been found that the gene name SQSTM1 it the culprit here to cause Interferon-induced RANK signalling and osteoporosis thus the neoplasia formed. By studying the genomic sequencing from the osteosarcoma germline it was seen that there are single nucleotide variation or structural variation of the TP53, RB1, ATRX, DLG2 gene locus.

Transcriptome and genome analysis shows that rearrangements of TP53, RB1, MDM2 and CDKN2A, as well as PMP22-ELOVL5 gene fusions and the most frequent TP53 rearrangements (e.g., TP53-VAV1, TP53-EMR1, TP53-PPRAD and TP53-KPNA3), resulted in the inactivation of p53 in osteosarcoma as well as the cessation of cell death in osteosarcoma.

Epidemiology: Osteosarcoma is neoplasia in long bones and is usually reported with 4.7 per million cases per year and 8.9% of lethality rate. As it is a childhood and pubertal disorder, the chances of healing increase by near about 65 percent. It has been seen from the genomic study of osteosarcoma that African American and Latino populations are mainly affected from the disease. Sometimes osteosarcoma can occur for the radiation applied to treat other types of cancers. Mainly long bones are affected like humerus, radioulna and tibiofibular effects with maximum occurrence in femur with 42 percent. A very few 1.25% of osteosarcoma are found in the ribs and fingers.

Classification: The disease can be classified based on the degree and duration of tumor growth, it can be categorized as high grade, intermediate grade, and low grade. Based on the nature of the pathogenesis and location of tumor it can be Osteoblastic (tumor cells may be osseous), Chondroblastic (tumor cells may be cartilaginous) and Fibroblastic (fibrous tissues may affect) [1, 9].

A tumor, which is of large blood-filled mass separated by thin bone, is called Telangiectatic [10]. If fibrous stroma is embedded with osseous matrix, they are generally termed as Desmoplastic fibroma; it can be seen in the jaw and pelvic bones. It has a slow growth rate but with aggressive characteristics. Extraskeletal osteosarcoma grows as a painless tumor in the soft tissue and then produces osteoid.

The types mentioned above of osteosarcoma are high-grade osteosarcoma that metastasize fast to other body parts. Periosteal Osteosarcoma is of intermediate grade and arises from the inner layer of periosteum. Periosteal Osteosarcoma is a low-grade variant of osteosarcoma that occurs on the outer protecting membrane of long bone and remains localized. The paget disease can become malignant and form Osteosarcoma [11].

Symptoms: Symptoms of osteosarcoma are bone pain, sprain, and lump formation; pain increases during physical activity, fever, and paralysis. It is reported that pain increases in night with walking difficulties that leads to pathologic fractures, sometimes associated with telangiectasia. In osteosarcoma, there is a chance of rapid growth of bone. In low grade, tumor develop at its place and reside locally; inlung metastasis respiratory symptoms like cough, excess mucous formation, wheezing, and chest pain are found.

Osteosarcoma has low background frequency with some other disease. Fibrosarcoma can be diagnosed histologically by the presence of fibroblast tissue that invade long bones Osteoblastoma is a large osteoid with vascular lesions.

Lymphoma, which increases lymphocyte formation uncontrollably, causes Hodgkin disease for middle-aged population and non-hodgkin disease for older population. There are some sarcomas like Ewing sarcomain which the reason is still unknown [1, 2].

Diagnosis:

Physical Examination: Physical examination shows that the patient has stiff joint, localized pain and warmth, lump, palpable mass, and pathological fractures of some patients; and some characteristic symptoms of cancer like unwanted weight loss, fever, malaise also appear.

Laboratory Diagnosis of Lactate Dehydrogenase (LDH) and Alkaline Phosphatase (ALP): LDH & ALParetwo Biochemical markers are assessed in the initial diagnosis. ALP levels become elevated by around 40 percent because of the increased osteoblastic activity often associated with osteosarcoma; levels may lower with treatment or rise with residual disease or recurrence [11].

X-ray: X-ray views of the suspected lump area of the whole bone and nearby joints show contusion at the metaphysis of the long bone; Diagnosis with an X-ray followed by a biopsy can confirm the osteosarcoma diagnosis, X-Ray of the chest should also be done to assess the lung metastasis

Magnetic Resonance Imaging (MRI): MRI is used to assess details of the contusion and invasion and its extension into the bones and soft tissue and vascular and neural structures of it; skip metastasis which are fragments of bone tumour present in some distance from the primary tumour. MRI with contrast revel those tumours which are situated within intra-articularly.

Computed Tomography (CT): Scans are useful in biopsy planning and reveal abnormal irregularities, fracture and mineralization in cortical bones. The extant and stage of tumour invasion is accurately detectable by MRI. Positron emission tomography scans can detect the primary metabolic sites and also detect metastatic, and has obvious advantages in showing osteosarcoma. Periosteal reactions are not well visible through CT [12].

Biomarker: There is only one biomarker that is helpful to diagnose the phenotype of osteosarcoma called SATB2 but is only helps to identify the osteoblastic phenotype but is incapable to determine the neoplasia is categorized under malignant or benign [14].

Biopsy: Biopsy is an essential procedure after diagnosis, laboratory tests to confirm the presence

of a lesion of osteosarcoma. This procedure helps to avoid timely detection and treatment of patients. The surgical procedure must have abscission of the biopsy tract, for identification. Analysis of Biopsy sample gives more accurate knowledge of the pattern and development of lesions. The common biopsy method is incisional biopsy and trucut biopsy. Puncture biopsy is usually performed for 2–10 min to cease the bleeding. Biopsy should be carefully approached to suppress the chances for the tumor cells to spread in the biopsy tract and nearby other tissues [12, 13, 15].

Stages of Tumor: Orthopaedic surgeons are concerned with the anatomical position of the tumor; whether the tumor is within the bone or outside of a bone. They are also concerned with the tumor's size, treatment response, and overall survival. Tumor in Stage IA is low grade, intracompartmental tumor location with no involvement in regional lymph nodes and no metastasis. in Stage IB it is also low grade, extra compartmental tumor location with no involvement in regional lymph nodes and no metastasis. Stage IIA consist of High grade, intracompartmental tumor location, regional lymph nodes are free from tumor spreading and no metastasis. Stage IIB is High grade, extracompartmental tumor location, no regional lymph node involvement no metastasis. Stage III is any grade, any location, metastasis present. Stage IVA: Tumor grade and size could be anything but no lymph node involvement, lung metastasis; Stage IVB: Metastasis in regional lymph node, lung or extra pulmonary region [13].

Treatment:

Surgical Method: Tissue of Osteosarcoma can be completely excised surgically with a wide safety margin; there are two approaches, limb salvage and amputation, for removing the lesion and its trace to prevent residual disease. Limb salvage is a surgical procedure that provides a safe way to treat Osteosarcoma. Limb salvage is consisting of resection and reconstruction. The resection intends to eliminate the primary biopsy site. Diagnostic imaging technology, such as bone scan, should be used to determine the quantity of bone to be resected to prevent residual disease; the recurrence of disease is due to poor response of disease. Resection followed by examination of that part to see the effect of chemotherapy on that tumor.

The process of reconstruction is mainly utilized for those bones which can carry heavy weight. Reconstruction surgery is two endoprosthetic types replacement and biological reconstruction. The first one is a form of limb salvage reconstruction with good functional outcomes [15, 16]. There are some challenges for the surgical procedure, such as excision followed by physical resection, which leads to an interruption in the child's growth and maturity.

In knee osteosarcoma surgery, the mass around the joint creates an obstacle for the surgeon; resection followed by tissue regeneration has overcome this challenge. Metallic prosthetics brought new light to surgical reconstruction; it provides large bone and joint replacement. The incidence rate of recurrences in local area after amputations and limb salvage are more or less similar; still, limb salvage patients have a higher 5-year survival rate. Limb salvage surgery protects the structural and functional integrity of the patient. The surgery should eliminate the lesion to prevent local recurrence and distant metastasis. If not the recurrence rate can increase up to 25%

There are few complications in the Prostheses, like local or systemic infections, which are frequent. The prevention for it is antibiotic therapy during lengthy surgery; systemic antibiotics are used and after surgery, local antibiotics are used [17]. When reconstructing the joint surface, the allograft prosthetic combination can be used to reconstruct the more stable per articular soft tissue by the allograft and the prosthetic side create the more stable joint articulation.

Chemotherapy: Chemotherapy is used as an adjuvant osteosarcoma treatment to eliminate lesions and metastases that cannot be eliminated by surgery alone. Preoperative chemotherapy has been successfully applied as part of the hospital's neoadjuvant chemotherapy approach. It is a landmark in the treatment of osteosarcoma; the chemotherapeutic drugs for OS are adriamycin, methotrexate, cisplatin, and ifosfamide; all of these drugs have significant efficacy. Combining those drugs with the different doses and frequency of administration can produce an effective chemotherapy regimen; *e.g.* Combination of Cisplatin and Doxorubicin (first line) Adjuvant

MAP therapy is composed of Methotrexate, Adriamycin, Cisplatin. Preoperative chemotherapy is given 2–6 cycles for 6–18 weeks [14]. If the chemotherapy is responded well less than 10% tumor content, that patient would continue their regimen; and Prescriber must change the combination of drug of patient with poor response The adverse effect of that chemotherapy include suppression of bone marrow, neurotoxicity, nephrotoxicity, hepatotoxicity, gastrointestinal disturbances. A side effect of chemotherapy treatment-related processes are included nausea, vomiting, pain at the site of chemotherapy, alopecia *etc* [12, 18, 20].

Radiotherapy: In non-metastatic osteosarcoma, local radiotherapy may create a positive impact. Studies found that external beam radiation therapy with systemic therapy or induction chemotherapy may relief local symptom. It is used for patients who cannot undergo resection or post- operative patient whose cancerous tissue is not incompletely removed. SRS (stereotactic radiosurgery) can be used in metastatic disease with Samarium 153-EDTMP. Side effect of radiation include dryness of skin and inside of the vagina (in case of brachytherapy), dry mouth, itchiness which can be ameliorate by hydration, menstrual cycle changes *etc* [19, 20].

Immunotherapy: Body's immune system consist of innate immunity that is the natural immunity of body and adaptive immunity which is the slow but long established immunity. In adaptive immunity T- cells plays the major role. In cancer therapy T-cells are utilized in the cancer cell vaccine. Dendritic cell is an antigen found on T-cell, collected from patient's blood used as cancer vaccine that has ability to slow down cancer progression [20].

Chimeric Antigen receptor T cells (CAR T-cells) are genetically modified T cells are injected in HER2 positive patient in a trial, after 12 to 15 weeks of treatment most of the patient shows stable response which means tumor size is not increasing by 20% nor decreasing by 20% Immuno-suppressive protein PD1 which is a Programmed death protein reside on the T cells and B cells. It induces treatment resistance. Programmed cell death ligand 1 (PDL1) is its ligand. PD1/PDL1 is overexpressed in the tumor microenvironment and it is an immune checkpoint that cause treatment resistance. Inhibiting PD1/PDL1 checkpoint pathway can be a promising therapy for cancer treatment. Recent Clinical trial of PD-1 inhibitor camrelizumab shows a positive response in lung metastasized osteosarcoma treatment, without showing a serious toxicities [20, 21].

Gene Therapy: Genetic mutation is the foremost reason of osteosarcoma. Gene therapy attempt to replace the defective or mutated genes with normal gene through a viral or non-viral vector that produce beneficiary effect. In the case of cancer, It results from a series of genetic alterations like rearrangements of one base, or deletion. So the target is the pivotal gene example p53 or pRb in the series of gene alteration in cance. P53 gene it can cause increase chemotherapy sensitivity, and it is a biomarker of the patient's overall survival. The study of thymidine kinase and propoxyguanosine approach in osteosarcoma's cell line can induce apoptosis and hinder the growth of the tumor cell line. This synergistic gene therapy improves the condition significantly. Combining other treatment methods with this gene therapy can be a good strategy in treating Osteosarcoma patients [21, 22].

Phytochemicals: Some plant-derived compounds have anti-tumor properties, and they can potentially undergo clinical trial as a supplement of standard chemotherapy treatment. For example, Curcumin is a natural polyphenol derived from curcuma longa. It can potentially induce apoptosis by activating various genes like MG63, U2OS, and HOS. *Genistein* is an isoflavonoid isolated from *Genista tinctoria*. Song and colleagues investigated that Genistein affects the PPARγ signalling, which negatively impacts Osteosarcoma proliferation. It also inhibits MG-63 genes, which is associated with osteosarcoma. Osteosarcoma's growth is reportedly suppressed by another phytochemical called bebeerine; it causes down regulation of caspase-1 and IL-1β in the osteosarcoma tumor. Bebeerine also reduces expression of E-cadherin, which is high in Osteosarcoma [14].

Follow-up & Monitoring: Post-operation, follow-up visits for the patient would be in every three months for 1 to 2 years; after that in, every four

months for 3years, then every six months for 4 and 5 years; from the sixth post-operative year, follow-up visit would be once in a year. The follow-up visit should include the physical assessment and Quality of Life (QOL) questionnaire. Imaging the site of operation and thorax through PET CT, CT scan, or bone scan to detect any lung lesions and pathological tests should include Complete Blood Count (CBC), Liver Function test, and Alkaline Phosphatase test. If any lesions or relapses are detected, the physician should start chemotherapy, resection, or palliative radiation, depending on the patient's condition [15].

Prognosis: The young adultpatient population has higher survival rates than the middle-aged patient population (over 40 years old); patients in the middle age group are more vulnerable to metastatic lesions in axial skeleton. Patients in the age group of 60 years or beyond, their body show refusal of surgery or chemotherapy. Osteosarcoma patients with pathological fractures cause an increase in mortality. Chondroid tumor indicates unfavourable in histology, whereas fibroblastic tumor shows good response. Different studies found that Men show higher chances of recurrence than women because of their less sensitivity for chemotherapy, which increase morbidity. Biomarker like Alkaline phosphatase (ALP) and Lactate dehydrogenase (LDH) are two important biomarkers for the Osteosarcoma patient. ALP promotes bone mineralization and associated with bone resorption, this biomarker may be or may not be in a normal level in the time of diagnosis, but it is elevated later on in Osteosarcoma patient. Serum LDH becomes higher in level in metastatic patients. The survival rate of Osteosarcoma patients also depends on the location and volume of tumor. Suppose tumors are diagnosed in the bones of skull, neck, vertebrae, sacrum and tailbone region. In that case, that means axial skeleton shows a worse prognosis than those in the bones of the shoulder, pelvis, arms, and leg region, which means the appendicular skeleton. Tumors with larger volumes cause a lack of response in chemotherapy, leading to recurrence [11].

DISCUSSION: Progress in treating osteosarcoma are slowly but steadily being made. Scientists are developing new approaches like immunotherapy, Gene therapy and combining these treatments with the old treatment regimen that are surgical methods and neoadjuvant chemotherapy; It can improve chemotherapy resistance. This combined treatment regimen increases the patient's progression-free survival and improves the overall quality of life. There has been a proposal of a new reconstructive method using liquid nitrogen that destroys tumor cells and after that patient's new cell replaced those cells. Frozen autograph method is a surgical procedure in which osteotomy, freezing the neoplast with liquefied nitrogen, and again moulding with plates termed arthroplasty. Frozen autographs can be a cost-saving method, and their effectiveness must be further studied.

Precise and early diagnosis is the key to the treatment. There are some concerning aspects that need to be improved, especially lung metastasis.

CONCLUSION: The synergism of different treatment strategies can produce optimum results in patient's body and it became the research interest. We believe that in the hence forward OS can be treated more holistically, and patient's quality of life will be improved.

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