Clinical Impact of the Phytoconstituents: An Emerging Frontier in the Treatment of Osteosarcoma




Khushali Nathani[1], Madhura Mulkutkar[1], Vandana S. Nikam[2], Sujata P. Sawarkar[1]*

1Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, V. L. Mehta Road, Vile Parle West, Mumbai 400056 India.
2 Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, India

sujata.sawarkar@bncp.ac.in

1. Introduction:

All the vertebrates including the human beings rely on bones; a sturdy, rigid, structural framework which supports and protects the internal body organs from all kinds of mechanical and physical shocks. Osteosarcoma is one such malignant form of bone tumor recorded to have 3.4 cases per million people annually (1). The observation over several years of research shows its prevalence majorly in the adolescents and children owing to the reason that the growth and hormonal changes are rapid during puberty and in geriatric patients having an underlining condition like Paget disease and secondary lesions (2). Osteosarcoma stems from mesenchymal tissue whose role involves production of bone like tissue from the stromal cells (3). The pathophysiology of the cancer involves the metaphysis region of the long bones of the skeletal system with common location in the femur, tibia and humerus and skull, jaw, pelvis being the potential sites. It is mainly classified depending on the location as Central (Intramedullary), Surface (Periosteal) and extra skeletal osteosarcoma (4). The microenvironment of osteosarcoma involves infiltration of immune cells creating a favourable immunosuppressive microenvironment boosting the abnormal growth of osteosarcoma cells within the bones (5). The primary function of osteoclast is the bone resorption; which on osteosarcoma invasion leads to osteolysis resulting in release of inflammatory markers like TGF-β, Interleukin-6, Interleukin- 11 from matrix of the bone which is degraded stimulating further the invasion and release of the inflammatory cytokines (6). Accurate diagnosis and stage of the cancer involves screening methods like X-Ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, Positron Emission Technology (PET) scan. All the imaging techniques have been advantageous in detecting the location of tumor, evaluated extent of tumor involvement and an edge of having able to detect complexities in tumor, overlapping parts (2). Apart from the imaging techniques the gold standard method for the diagnosis.

2. Current Treatment Approaches:

2.1 Surgery

Surgical intervention still remains one of the treatment approaches for osteosarcoma with 5-year survival rate of upto 23%. (7) The various surgical approaches involve amputation of limbs, limb salvage surgery, limb reconstruction using grafts. The selection of the surgical methods relies on various factors like response to chemotherapy, location of tumor and extent of metastasis. Amputation is no more primary choice of the orthopedics owing to complications involved. The aim is to preserve and restore the limb's structural and functional capacity which can be achieved by limb salvage surgery who have higher rate of survival. Limb reconstruction on the other hand consists of autografts and allografts which is a scaffold like structural framework aiding in limb growth (7).

2.2 Radiation Therapy

For the patients in whom surgical procedure is complicated or in cases when chemotherapy shows poor response, the alternative therapy for the cancer patients is by radiation. They are basically electrically charged particles known as ionizing radiation (8). The principle involves deposition of the radiation comprising of high energy passing via the cancerous cell resulting cell death followed by genetic changes (8).

2.3 Chemotherapy

The main objective of chemotherapy involves inhibition of tumor angiogenesis by inhibiting cell proliferation and multiplication circumventing the chances of metastasis (9). Earlier traditional chemotherapy being less effective in terms of drug resistance leading to delaying cell death, the current treatment involves the use of combination chemotherapy decreasing likelihood of drug resistance, along with dose reduction further decreasing side effects (9).

3.Gene Therapy

The new modality which involves introducing healthy cell as vector into cancerous cell (10). Gene therapy is transferring of foreign DNA into the human cells with aid of vectors. Gene therapy may not be effective on its own, but it may require to be combined with presently used chemotherapeutics to improve tumor mortality and patient survival.

4. Need of Phytoconstituents:

The present approaches for the treatment of osteosarcoma have poor patient outcomes. Antineoplastic drugs are used at high doses for the chemotherapy which result in acute and chronic side effects. Furthermore, tumor metastasis has shown to decrease the survival rate to 30% (11,12). Therefore, it is imperative to discover novel antineoplastic drugs to enhance patient response and patient outcomes (13). The upcoming arena of gene therapy has shown promising results in the preclinical stage however, the clinical translation has many ethical and economical challenges. Most anticancer molecules in the clinic are derivatives of phytoconstituents. With promising therapeutic efficacy, these phytoconstituent derivatives are popularly being used as first-line treatment options for various cancers. Following suit, many researchers have found that phytoconstituents can be used for managing osteosarcoma as well. These molecules can either serve as new antineoplastic entities or as scaffolds for designing novel anti-cancer compounds.

Table 1: Phytoconstituents for treatment of Osteosarcoma

PHYTO-CONSTITUENT	DOSE	CELL LINE	EFFECT	REFERENCES
Curcumin (Flavonoid)	15 µM	U2OS	Proliferation, migration, invasion suppressed, apoptosis induced	(14)
	10-40 µM	U2OS, MG-63	Cell death induced, inhibit invasion and proliferation	(15,16)
	6-50 µM	MG-63, HOS, MG-63 M8, LM5, Hu09, SAOS2	Induced apoptosis, inhibit growth, proliferation and migration	(17)
	5-10 µM	MG-63	Autophagy, Hypoxia induced proliferation	(18, 19)
	5-25 µM	U2OS, HOS	Cell Viability decreased	(20)
Genistein (Isoflavone)	40 µM 60 µM 80 µM	MG-63	Inhibition of osteosarcoma cell growth	(21)
	-	MNNG, HOS	Inhibition of cell growth, Apoptosis	(22)
	100 µM	SaOS- 2, MG-63	Proliferation induced and reduced	(23, 24)
	10 µg/ml	CVCL W629	Motility of cells reduced	(25)
Biochanin A	10-30 µg/ml	MG-63, U2OS	Apoptosis, cell growth is inhibited	(26)
Quercetin (Flavonoid)	50 µM	U2OSPt	Inhibit proliferation	(27)
	100-200 µM	MG-63	Cell death by triggered autophagy	(28)
	5-100 µM	D-17, DSN	Suppress cell proliferation	(29)
	20-100 µM	U2OS, SaOS-2, HOS, MG-63	Decrease cell proliferation, invasion of tumor cells, migration	(12, 30)
	10-100 µM	143B	G_2/M phase cell cycle arrest	(31)

Most anticancer molecules in the clinic are phytoconstituents or their derivatives. Likewise, a number of publications cite the application of phytoconstituents for osteosarcoma.

Resveratrol (Flavonoid)	10 µM 20 µM 40 µM	hFOB1.19, MNNG/HOS, U2OS, MG-63	Cell Renewal capacity, Inhibit proliferation	(32, 33, 34)
	6 µM 12 µM 18 µM 24 µM	U2OS	Glycolysis inhibited, avoid invasion	(35)
	50 µM	SaOS- 2	Hypoxia induced proliferation	(36)
	10-100 µM	SJSA1	Inhibition of osteosarcoma cells	(37)
Tanshinone IA (Terpenoid)	10 mg/kg 20 mg/kg	-	Suppress tumor growth	(38)
Tanshinone IIA (Terpenoid)	0-20 mg/L	MG-63	Autophagy	(39)
Galangin (Polyphenol)	-	MG-63, U2OS	Anti migration, pro-apoptotic, anti-proliferative	(40)
Silibinin (Flavonolignans)	-	MG-63	Reduced adhesion and invasion of osteosarcoma cells	(41)
Berberine (Alkaloid)	20-80 µM	MG-63	Cell proliferation and migration inhibited	(42)
	25 µmol/L 50 µmol/L 75 µmol/L 100 µmol/L	MG-63	Cell cycle arrest, Apoptosis, Radiosensitivity promoted	(43)
	12.5-50 µg/ml	U2OS	Suppression of proliferation	(44)
	80 µM	MG-63	Inflammation modulation around tumor	(45)

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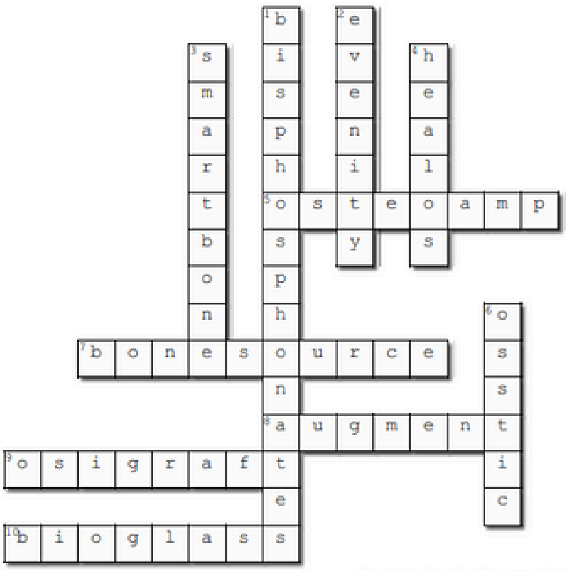
Fun & frolic - Crossword Solution



Created using the Crossword Maker on TheTeachersCorner.net

Across

5. Commercial Allogeneic-derived Scaffold (**osteoamp**)
7. Calcium cement-based product (**bonesource**)
8. Commercial collagen/tricalcium phosphate scaffolds (**augment**)
9. Medical Device (**osigraft**)
10. Silica-based biomaterial used for synthetic bone grafts (**bioglass**)

Down

1. Agents targeting hydroxyapatite (**bisphosphonates**)
2. FDA approved bone-building humanized monoclonal antibody (**evenity**)
3. Commercial biohybrid graft (**smartbone**)
4. Marketed collagen/hydroxyapatite composite (**healos**)
6. Bioceramic glue (**osstic**)

Fun & frolic - Match the Column

Write the letter of the correct match next to each problem

1. ______	Alen	a.	Selective estrogen receptor modulators
2. ______	Odanacatib	b.	Bone disease
3. ______	Raloxifene	c.	Cathepsin K inhibitor
4. ______	Osteoporosis	d.	Functional ligands for bone targeted delivery

Solution on page 19