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Hematological Toxicity Induced by Bone Metastasis Radiation Therapy

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Cite this chapter as: Vazquez L, Arnaud A. Hematological Toxicity Induced by Bone Metastasis Radiation Therapy. In: Sergi CM, editor. Metastasis. Brisbane (AU): Exon Publications. Online first 2022 Mar 19.

Doi: https://doi.org/10.36255/exon-publications.metastasis.hematological-toxicity

Abstract: Radiotherapy is frequently used in patients with bone metastasis. However, radiotherapy for bone metastasis may cause clinically significant hematological toxicity both by depleting the blood cells and by damaging the proliferating bone marrow. In general, lymphocytes (T cells, B cells and natural killer cells) are among the most radiosensitive cells, followed by monocytes and macrophages. As the most radiosensitive cells in the hematopoietic system, radiotherapy-induced lymphopenia occurs immediately after irradiation and shows a nadir within 1–2 months after the initiation of radiotherapy. Radio-induced hematotoxicity is a significant clinical problem affecting treatment outcome and survival of cancer patients. This toxicity results from the direct effects of radiation on circulating lymphocytes and the indirect effects on stem cells in the bone marrow.

Keywords: bone marrow toxicity of radiation therapy; bone metastasis; hematological toxicity of radiation therapy; radiation therapy for bone metastasis; stereotactic body radiation therapy

In: Consolato M. Sergi, editor. *Metastasis*. Exon Publications, Brisbane, Australia. ISBN: 978-0-6453320-2-5. Doi: https://doi.org/10.36255/exon-publications.metastasis

INTRODUCTION

Bone is one of the most common sites of metastasis from advanced solid cancers. Bone metastases occur in 65–80% of patients with advanced prostate or breast cancer, 40–50% patients with lung cancer, and in <10% of those with gastrointestinal cancer (1–3). The bone is a dynamic tissue that contains minerals and houses the bone marrow. The principal cells of bone tissues are osteoblasts and osteoclasts that maintain structural integrity, and osteocytes that regulate bone remodeling. Metastases preferentially occurs in trabecular bone and bones rich in red marrow, suggesting that some bones provide a better environment for metastatic growth (4). Several tumor-bone marrow microenvironment interactions, such as, osteoclastic bone resorption, osteolysis, vessels formation, and platelet function alteration, promote metastatic tumor implantation and growth by direct and indirect stimulation (5).

BONE METASTASIS: EFFECT ON PATIENT

In general, the overall result of increased tumor burden in bone in metastatic cancer is osteolysis (breast, renal and other cancers) or osteosclerosis (prostate cancer) (6). Tumor cells in the bone microenvironment disrupt normal bone physiology, resulting in increased growth factor release (TGF-β, PDGF, FGF, VEGF, IGF) from the mineralized bone, which in turn enhances tumor cell growth and further bone disruption (7). This cyclic relationship increases metastatic lesions in the bone and leads to numerous adverse conditions such as bone fracture, hypercalcemia, and compression of the spinal cord. Bone marrow and periosteum are richly innervated tissue with abundant nociceptors—mediators of acute and chronic bone pain. Indeed, cancer-related pain is the most common consequence of bone metastases. Although metastatic bone disease could be asymptomatic in some cases, it has been estimated that at least 75% of cancer patients with bone metastases present with bone pain (8), significantly degrading functional status and mobility, and quality of life. Bone marrow metastasis from solid cancers can also cause hematologic disorders. Disseminated intravascular coagulation and/or microangiopathic hemolytic anemia are the most serious disorders, increasing susceptibility to infection and reducing the patient's survival prognosis (9).

THE BONE MARROW

Bone marrow, the primary site of hematopoiesis (new blood cell production), is composed of hematopoietic cells, marrow adipose tissue, and supportive stromal cells (10). In the skeleton, two bone marrow types have been identified with distinct composition and vascularization: yellow and red. The yellow bone marrow, mainly in the appendicular skeleton, is composed of adipocytes. Contrary to the yellow bone marrow, red bone marrow is responsible for

blood cell production. A large network of sinusoids allows vascularization. Red bone marrow is mainly found at the ends of the long bones (near the joints of healthy adults) and also in the skull, the sternum, the scapulae, the vertebrae, the ribs, and the pelvic bones (11). Bone marrow comprises approximately 5% of total body mass in healthy adult humans (12). Human marrow produces approximately 500 billion blood cells per day, which join the systemic circulation via permeable vasculature sinusoids within the medullary cavity. All types of hematopoietic cells, including both myeloid and lymphoid lineages, are created in bone marrow; however, lymphoid cells must migrate to other lymphoid organs (e.g., thymus) in order to complete maturation.

[18F] FLT PET is a promising imaging modality to identify active bone marrow. It can identify proliferation in tumors, reflecting the level of cells undergoing DNA synthesis. Agool et al. showed a correlation between [18F] FLT PET and bone marrow activity (13) whereas Hayman et al. used it to quantify the relative distribution of active bone marrow throughout the body (14). Consequently, [18F] FLT PET could identify active regions of bone marrow in the pelvis. The doses received by the active volumes of the bone marrow could be identified precisely. From this, a correlation between the irradiated active volume and hematological toxicity can be determined. Knowledge of this correlation would make it possible to institute dose limits and therefore plan treatment to avoid bone marrow toxicity during radiotherapy.

RADIATION THERAPY IN BONE METASTASIS

Radiation therapy is an effective treatment option for bone metastasis because of its capacity to reduce tumor size and to relieve pain. Radiation therapy can also promote ossification of osteolytic lesions, stabilizing the affected bone (15). A recent study shows that external-beam radiation therapy provides complete pain relief in 24% of patients, and 50% pain relief in 41% of patients (16). Two-dimensional radiation therapy (2D-RT), and three-dimensional conformal radiation therapy (3D-CRT) are the most common external beams radiation techniques used for bone radiation therapy. To decrease potential treatment toxicity, several modern techniques like intensity modulated radiation (IMRT), volumetrically modulated arc therapy (VMAT), or tomotherapy are used. These techniques allow to spare healthy tissue by offering more precise tumor contouring. More recently, even more precise irradiation techniques such as stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) have been developed (17). Their use in clinical practice is not yet possible for all tumors masses and depends on several factors such as patients-related factors (performance status, mobility, life expectancy, compliance, pain intensity), tumor-related factors (histologic type, neurologic deficits, multiplicity of metastases) and logistic issues (treatment duration, distance from patient's home). However, there is still no standard treatment for painful bone metastases. Generally, bone metastases are multiple, and only 11% of patients with bone metastasis have only one bone metastasis (18). Many studies have attempted to

assess the best strategy in terms of dose and fractionation for the management of pain from bone metastases. Different schedules have shown equivalent analgesic effects and efficacy: a single 8 Gy fraction, 30 Gy delivered in 10 fractions, 24 Gy in 6 fractions, or 20Gy in 5 fractions (19).

EFFECT OF RADIATION ON BONE MARROW CELLS COMPONENTS

The bone marrow is composed of two types of multipotent stem cells: hematopoietic stem cells and mesenchymal stem cells. Hematopoietic stem cells give rise to myeloid (neutrophils, eosinophils, basophils, monocytes, macrophages, erythrocytes, and thrombocytes) and lymphoid (T lymphocytes, B lymphocytes, NK lymphocytes [natural killers]) lineages forming the immune system (20). Mesenchymal stem cells differentiate into adipocytes, osteoblasts, and chondrocytes. These two types of stem cells (hematopoietic and mesenchymal) are in the same niche or functional unit and are dependent on each other for their survival (21). Mesenchymal stem cells secrete growth factors controlling the proliferation and differentiation of hematopoietic stem cells or their maintenance in a multipotent state (22). The bone marrow is made up of a multitude of functional units; it is therefore considered as a parallel organ. Therefore, the effects of irradiation on the bone marrow must be considered according to the dose delivered and the volume irradiated (23). Each of these cells has a different radiosensitivity. Mesenchymal stem cells are usually resistant to irradiation via various pathways including the phosphorylation of the ATM protein, activation of the cell cycle checkpoint, and repair of DNA double strand breaks. Hematopoietic stem cells, like all cells with a high proliferative potential, are sensitive to radiation or chemotherapy agents (24, 25).

The critical dose below which a fraction of the irradiated bone marrow regenerates constantly, and the dose above which no marrow regeneration is possible are subject to debate. It depends on many factors such as fractionation, dose rate, irradiated site, irradiated volume, adjuvant or neoadjuvant chemotherapy, history of irradiation, and the oncological status of the patient (bone metastases, bone marrow invasion, etc). In a patient unaffected by previous treatment, a dose of 30 Gy delivered in a normofractionated manner still allows bone marrow regeneration (5). Beyond 30 Gy, the portion of irradiated bone marrow does not regenerate, and the adjacent portions compensate for the lack of hematopoietic activity. However, if the dose received is less than 50 Gy and the volume of marrow irradiated is greater than 50%, partial regeneration of the hematopoiesis occurs. Beyond 50 Gy, the marrow microenvironment is destroyed, and reactivation is impossible (26). The impact of dose rate on marrow regeneration has not been clearly studied in humans; most of the studies are in vitro studies or studies carried out on animal species (27). The most common hematotoxicities of metastatic bone irradiation are summarized in Table 1.

TABLE 1 The most common hematotoxicities of metastatic bone marrow irradiation

Direct effects	Circulating lymphocytes (28)	Radiosensitive	Lymphopenia	Defective immune response
Indirect effects	Hematopoietic Stem cells (29)	Radiosensitive		
	Myeloid cells	Sensitive ++	Progenitor cells depletion	Anemia Infection
	Lymphoid cells	Sensitive +++		Defective immune response
	Mesenchymal Stem cells (30)	Radioresistant		
	Adipocytes	Resilient +++	Adipocytes expansion	Poor bone architecture quality
	Osteoblasts	Resilient +	Bone loss	

CONCLUSION

Radiation therapy for bone metastasis can lead to radiation-induced hematotoxicity within 1–2 months of the initiation of irradiation. Hematotoxicity results from the direct effect of radiation on circulating lymphocytes, and also from the indirect effect of radiation on stem cells in the bone marrow. The irradiation of bone metastases in these areas must be carefully considered according to the risk-benefit ratio for the patient.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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