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The Effect of Bone Radiation on Hematopoiesis: A Literature Review

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Abstract

Over time, external radiation techniques have continued to evolve so that they can be used to treat bone malignancies for curative, postoperative adjunctive, and palliative purposes. However, the bone marrow is sensitive to radiation. Even sublethal doses can cause bone marrow microenvironment deficits, including a decrease in hematopoietic cells. There is a complex relationship between radiotherapy (RT) and the hematopoietic system. Acute radiation injury usually manifests as cytopenia: anemia, neutropenia, and thrombocytopenia. Several potential mechanisms regarding the effects of radiotherapy on bone marrow, including direct injury to the hematopoietic stem cells (HSC), lead to decreased number and function. This literature review will discuss hematopoiesis, the effect of bone radiation on hematopoiesis, and its mechanisms.

Keywords: bone, hematopoiesis, radiotherapy

Introduction

Radiotherapy (RT) uses high-energy rays or particles to kill cancer cells and is an important modality in cancer treatment, with at least 60-65% of all cancer patients will require radiotherapy as a single treatment modality and/or in combination with surgery or chemotherapy.[1] Over time, external radiation techniques continue to develop so that they can be used to treat inoperable bone malignancies where the tumor mass cannot be entirely removed by surgery. Radiation may also be given postoperatively in cases with positive margin. In this case, radiation may be given to kill any remaining cancer. If bone cancer reappears after treatment, radiation can help control symptoms such as pain and swelling.[2] Radiotherapy can also be given to patients with bone malignancies who refuse surgery.[3]

However, bone malignancies are not easily killed by radiation and high doses are required, so radiotherapy has a relatively minor role in the treatment of bone malignancies.[2,3] Radiotherapy more often acts as palliative therapy in cases of bone metastases to reduce pain and strengthen weight bearing bones so as to improve the patient's quality of life.[3,4,5]

Radiotherapy has a good effect in reducing pain due to bone metastases in almost 50-80% of patients. There are several variations of the dose fractionation scheme that can be given to bone palliative cases without a previous history of radiation; 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and single fraction with 8 Gy dose which provide good pain control with minimal side effects.[6]

The radiation dose given can damage the surrounding healthy tissue and other vital structures such as nerves, blood vessels, including the bone marrow.[2] The lymphohematopoietic system is the most radiosensitive

tissue, and radiation-induced suppression of hematopoiesis and immune function has been considered one of the most life-threatening consequences of radiation exposure.[7] Since the early 1900s, it has been known that ionizing radiation (IR) can damage hematopoiesis through various mechanisms. Radiation exposure directly damages hematopoietic stem cells and alters the capacity of bone marrow stromal elements to support and/or maintain hematopoiesis in vivo and in vitro. Exposure to IR has long been known to be associated with changes in hematopoietic tissue and can sometimes lead to death.[8]
Therefore, in cases with extensive metastases or lesions in many part of the body, the use of radionuclides is more suitable than external radiation. Hemibody radiotherapy is an option if radionuclide facilities are not available or there are contraindications.[6]
The ability to maintain the bone marrow microenvironment will prevent trabecular bone loss caused by radiation exposure, which in turn can cause several comorbidities in radiation-exposed patients.[9] In this literature review, we will further review the side effects and mechanisms of bone radiation on hematopoiesis.

Bone Marrow

Bone marrow (BM) is located in the interior of the skeleton and serves as the primary home for two populations of multipotent stem cells; hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC). HSCs are blood-forming hematopoietic stem cells and progenitor cells responsible for the production of blood cells in humans. MSCs produce bone, cartilage, muscles, tendons, ligaments, and fat cells.[9,10,11] The BM is also the fourth largest organ by weight, after bone, muscle, and fat. It is estimated that, in humans, bone marrow accounts for about 4-5% of total body weight.[11] There are two types of bone marrow that vary in composition and function: active hematopoietic marrow (red) and inactive hematopoietic marrow (yellow).[11,12]
Bone marrow is a highly radiosensitive tissue, and the distribution of active bone marrow changes with age. In children, active bone marrow is found in the sternum, ribs, pelvis, spine, skull, femur, humerus, and other long bones, whereas this distribution later focuses on the axial skeleton, proximal femur, and humerus. About half of the active bone marrow in adults is located in the pelvis and lumbar spine area (**Table 1**).[12,13]
HSCs and MSCs share the same niche in the bone marrow (**Figure 1**), and many of their lineage cells are responsible for maintaining that niche. Although MSCs and HSCs are found within the bone marrow compartment, they are not uniformly distributed and localized in a specific region. HSCs usually surround sinusoidal vessels and endosteal surfaces, and MSCs are found near HSC.[9,14]

Table 1. Distribution of bone marrow in an adult.
Source: reference no. 13

Location	Bone Marrow Distribution
Cranium	12%
Mandible	1%
Cervical spine	3%
Clavicle	1%
Scapula	5%
Sternum	2%
Ribs	8%
Thoracic spine	14%
Humerus	1%
Lumbar spine	11%
Os coxae	22%
Sacrum	14%
Femoral head/neck	4%

Hematopoiesis

Hematopoiesis is a process of forming cellular components of blood that begins from embryonic development to adulthood in order to produce and replenish the blood system.[15] The blood system contains several different types of blood cells (lineage) with various functions. All blood cell types are derived from HSCs, predominantly located in the BM, which is the leading site of adult hematopoiesis. Blood is one of the most regenerative tissues, and millions of "old" blood cells are replaced with new ones every second of life. The life span of various types of mature blood cells ranges from hours to years.[16]
Blood cell production originates from the focal islets of the extraembryonic yolk sac in the first week after

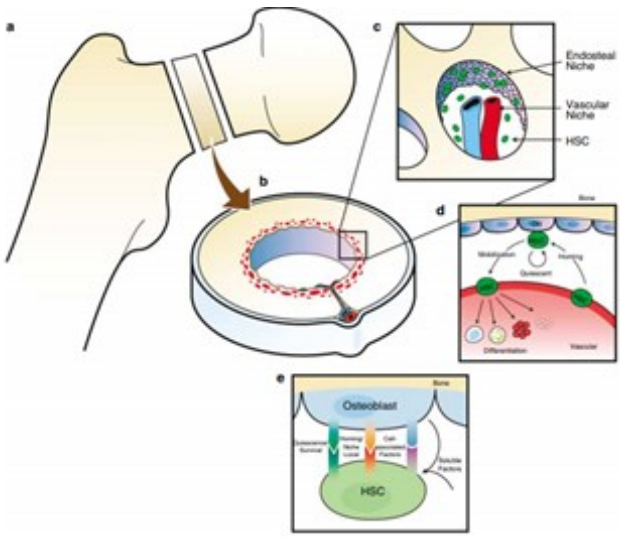

Figure 1. Model of the stem cell niche in long bones.
Source: reference no. 14

fertilization.[17] At about 5-6 weeks of gestation, progenitors derived from the yolk sac also colonize the fetal liver and become the primary source of blood cells for the remainder of intrauterine life. At about seven weeks of gestation, hematopoietic cells also colonize the spleen, and multipotent progenitor cells are seen in the fetal circulation at the end of 12-14 weeks of gestation.[18] Around 8–9 weeks, when hematopoiesis in the yolk sac becomes extinct, T cell production begins in the thymus. Hematopoietic cells first appear in the medullary cavity of the bone around 14 weeks of gestation, and after birth the bone marrow has become the primary site of hematopoiesis.[17]

The most apparent change seen in the bone marrow with age is a decrease in cellularity. Under normal circumstances, the bone marrow is the only site of hematopoiesis. Extramedullary hematopoiesis can occur in the liver, spleen, and lymph nodes in pathological conditions when the compensatory mechanisms of the marrow are exceeded.[19] By the age of 40, the bone marrow in the sternum, costae, pelvis, and spine consists of equal amounts of hematopoietic tissue and fat. At the age of 65 years, bone marrow cellularity is estimated to be about 30% with an increase in bone marrow fat.[17]

Mechanisms of IR-Induced HSC Injury

Several mechanisms of BM injury due to IR have been described; induction of HSC apoptosis and/or differentiation; HSC aging induction; and/or damage to BM stromal cells or HSC niche.[20,21]

Ionizing Radiation-Induced Apoptosis in HSC

Apoptosis is a form of regulated cell death through a genetically controlled process. Characteristics of apoptotic cells include externalization of phosphatidyl-serine on the outer leaflet of the plasma membrane, cell shrinkage, nuclear chromatin condensation, nuclear and DNA fragmentation, and cellular membrane blebbing.[22] In coordination with cell proliferation and differentiation, apoptosis contributes to the maintenance of hematopoietic homeostasis by regulating the size of the hematopoietic lineage. Dysregulation of apoptosis in hematopoietic cells can lead to many pathological conditions. It has been suggested that IR causes the induction of apoptosis in BM cells, including HSCs.[21] IR will activate p53 and induce Puma to block the interaction between antiapoptotic proteins (Bcl-2 and Bcl-xl) with proapoptotic effectors (Bax and Bak). Then, the mitochondria releases caspase-activating factors (cytochrome c and Apaf-1) which activates Caspase -3, -6, and-7 and results in the apoptosis of HSCs.[21]

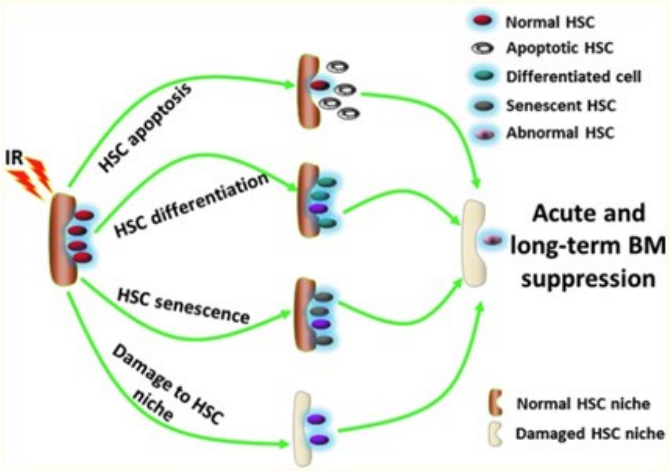

Figure 2. Mechanisms of IR-induced HSC damage and bone marrow injury.
Source: reference no. 21

Ionizing Radiation-Induced HSC Differentiation

HSCs not only have self-renewal ability but can also differentiate into various blood cell lineages. Both of these functions must be tightly regulated as inhibition of HSC differentiation can promote HSC self-renewal, which can result in abnormal HSC expansion and leukemia. In contrast, the promotion of HSC differentiation can decrease HSC self-renewal, which can lead to premature exhaustion of HSCs and BM failure.[23] Furthermore, the differentiation of HSCs to different blood cell lineages must be balanced to prevent lineage skew. An evidence suggests that DNA damage response (DDR) plays an essential role in regulating stem cell differentiation. For example, Lin et al. reported that induction of double-strand breaks by doxorubicin promoted mouse embryonic stem cell (ESC) differentiation in a p53-dependent manner. This is because p53 activation downregulates Nanog expression, which is required for ESC self-renewal.

Ionizing Radiation-Induced Aging in HSC

Normal human diploid fibroblasts have limited growth potential. The intrinsic replicative lifespan of cells appears to be determined by telomere length. Without telomerase expression, the telomeric sequence shortens each time the DNA replicates.[24] Moderate levels of telomerase activity were detected in HSCs. This activity is required to maintain normal HSC function because a lack of telomerase activity can lead to telomere shortening and decreased transplantability of HSCs. In addition, the development of aplastic anemia or bone marrow failure has been observed in patients with telomerase deficiency due to mutations in telomerase reverse transcriptase (TERT) or telomerase RNA component (TERC). However, TERT

overexpression in HSCs maintains HSC telomere length but fails to prolong HSC lifespan in the setting of serial BM transplants.[21]

In addition, many types of human and animal cells undergo aging after exposure to oxidative and genotoxic (including IR) stress. It also occurs when cells are subjected to oncogenic stress and/or aberrant activation of the p38 pathway. Aging caused by oxidative, genotoxic, and oncogenic stress is also referred to as premature aging to distinguish it from replicative aging. This is because cells that undergo premature aging due to stress have a shorter intrinsic replicative life without significant erosion of telomeres.[21]

Similarly, it has been hypothesized that IR and chemotherapy cause residual BM injury mainly by induction of HSC senescence, impairs HSC replication and self-renewal, leading to decreased HSC reserves. Disruption in HSC self-renewal has been well documented in patients and animals after exposure to total body irradiation (TBI) or treatment with various chemotherapeutic agents, leading to residual BM injury. Interestingly, the shortening of the intrinsic replicative capacity of HSCs or the loss of self-renewal of HSCs after IR exposure did not affect the differentiation of HSCs to produce various hematopoietic progenitor cells (HPCs) and more mature progeny before their final exhaustion. In addition, HPC from irradiated mice showed no abnormalities and also showed no signs of aging. These findings suggest that IR can selectively cause HSC senescence.[21]

Ionizing Radiation-Induced Damage to HSC Niche

IR-induced damage to various components of the HSC niche contributes to HSC injury and affects HSC recovery after IR. A large body of literature shows that IR induces BM stromal injury in a dose- and time-dependent manner, which has been reviewed extensively in previous publications. Induction of BM stromal cell senescence contributes to IR-induced residual damage in the BM environment that may influence hematopoiesis.[21]

However, the IR damage to specific components of the HSC niche and the impact of the damage on the HSC is unknown to date.23 IR-induced sinusoidal endothelial cell (SEC) damage may be mediated in part by activation of acid sphingomyelinase (aSMase), which induces endothelial cell apoptosis through increased ceramide production. Inhibition of SEC regeneration through blocking vascular endothelial growth factor receptor 2 in irradiated mice prevented hematopoietic recovery. In contrast, endothelial cell transplantation into lethally irradiated mice improved their survival by promoting HSC regeneration and hematopoietic recovery. Similarly, infusion of endothelial progenitor cells into irradiated mice accelerated vascular niche recovery and promoted HSC recovery. The mechanism by which SECs promote HSC reconstitution after IR remains elucidated but may be partly due to the expression of angiopoietin-like protein three and pleiotrophin. Compared with BM SEC, endosteal osteoblasts, a significant component of the osteoblast niche, are relatively radioresistant. After BM radio ablation, endosteal osteoblasts undergo rapid expansion in response to mesenchymal mesenchymal-derived growth factors such as platelet-derived growth factor-β and basic fibroblast growth factor to promote HSC formation and hematopoietic recovery after BM transplantation by restoring damaged HSC niches.[21]

Hematopoietic Effects

Radiation on bone malignancies, either definitive, adjunctive after surgery, or palliative affecting the bone marrow, will potentially cause a decrease in the number of blood cells due to the destruction of highly radiosensitive hematopoietic stem cells and progenitor cells. The more radiation dose is absorbed, the more hematopoietic stem cells and precursor cells die, and there is less or no more formation of functional mature cells.[25]

Radiation dose is a predictive factor in the hematological system and other body tissues. Doses < 2Gy can induce mild cytopenia without significant bone marrow damage.[26] Acute bone marrow injury occurring shortly after radiotherapy, associated with the induction of HSC apoptosis manifests as cytopenia: anemia, neutropenia, and thrombocytopenia.

The effect of IR dose (>1Gy) on mouse HSC has been extensively studied. After dosing of 2Gy, murine HSCs, not progenitors, activate p53, resulting in apoptosis. Quiescent HSCs repair damaged DSBs by non-homologous end joining (NHEJ), whereas circulating HSCs repair damage by homologous recombination. At higher doses (>4Gy), DDR in HSCs induces several effects; p53 activation, Puma induces apoptosis; activation of G-CSF/Stat3 which activates BATF thereby decrease self-renewal of HSCs and HSC senescence is associated with persistent reactive oxygen species (ROS) production which results in loss of self-renewal of HSCs without affecting HSC differentiation.[27]

This effect is most likely to occur with large volume radiation for example in the pelvic or spinal region,

which is the primary location of the functional bone marrow, accounting for about 60% of the total volume. Hematopoietic disorders also depend on the extent of the bone metastases in which the cranium, ribs, thoraco-lumbar sacral pelvis already cover more than 80% of the hematopoietic system.[28]

Unfortunately, most of the data for detailed hematopoietic effects of RT comes from exposure to a single large fraction of TBI or radiation administered to a vast field that is no longer used in routine practice.[28] Even very low doses of RT (as low as 0.3Gy) can cause measurable changes in peripheral blood counts (especially lymphocytes at this dose) due to the radiosensitive nature of these cells. Another source also said that low-dose radiation, which is 0.25 Gy, has also been able to cause changes in the formation of blood cells (hematopoiesis) with the result that changes occur either by direct damage to the hemopoietic tissue or due to the influence of neurohormonal mechanism.[28-30]

A study of bone marrow monoclonals (BM-MNCs) in the femur and tibia of mice using a colony forming assay found a significant reduction with exposure to doses of 50mGy in the acute phase and 250mGy in the chronic phase.[31]

At larger doses, lymphopenia usually occurs almost immediately due to radiation-induced apoptosis at interphase, followed by granulocytopenia, then thrombocytopenia, and finally anemia (**Figure 4**). Circulating platelets, with a life span of about ten days, progressively disappear from the blood over this period and are then replaced in varying degrees depending on the degree of stem cell damage. Anemia without acute bleeding is rare because of the relatively long age of mature red blood cells, which is about four months. Because it is highly radiosensitive, lymphocytopenia due to radiation-induced apoptosis occurs before other cytopenias occurs, within 6-24 hours after radiation exposure. B lymphocytes are more radiosensitive than T lymphocytes.[25,32,33]

After an intermediate dose of total body radiation, the initial cell count decreases at approximately 1, 4, 8, and 12 days for lymphocytes.[28,32] Lymphocytes are most susceptible to radiosensitivity, and peripheral counts drop immediately after low-dose radiation. Neutropenic nadir occurs next, within one week, followed by thrombocytopenia at 2-3 weeks and anemia at 2-3 months. Patients with severe hematological toxicity may require transfusion, erythropoietin, or growth factors to promote hematopoietic stem cell proliferation.[12] However, due to its ability to repair DNA damage, HSC undergo self renewing proliferation and differentiation to repopulate

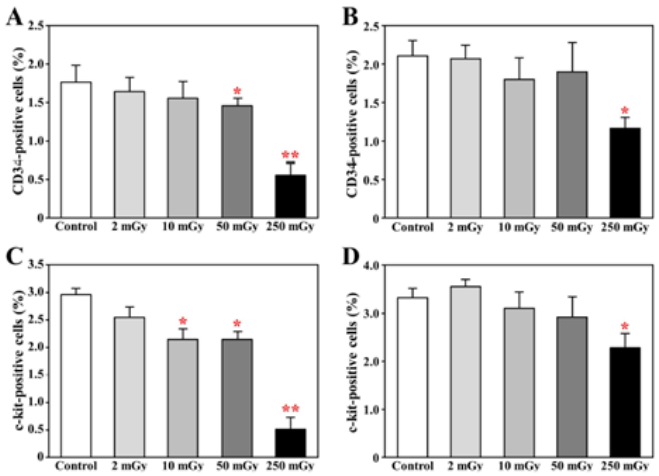

Figure 3. The number of HSCs in mice bone marrow after radiation exposure. Soon (A, C) or after 3 months (B, D) with daily radiation exposure of 2, 10, 50, and 250mGy.
Source: reference no. 31

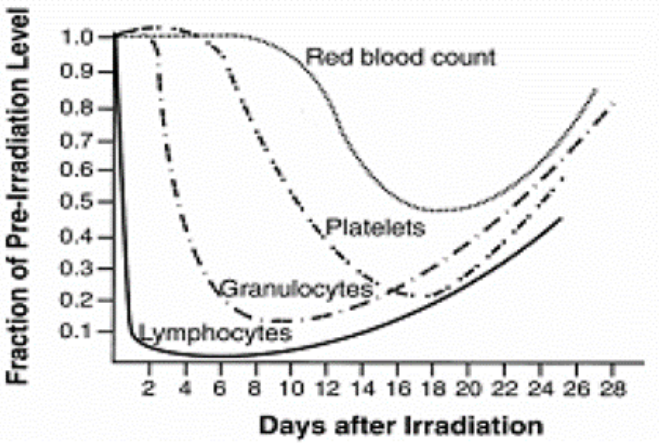

Figure 4. Response of hematopoietic tissue to radiation.
Source: reference no. 34

multipotent progenitor (MPP) and HPC which then regenerate mature blood cells to maintain homeostasis of the hemopoietic system.[20]

The long-term effects of high doses (cumulatively 30 Gy or 20 Gy in a single dose) of irradiation to bone marrow have been shown to vary according to what percentage of bone marrow is in the field. If less than 50% of the bone marrow is irradiated, the surrounding unirradiated bone marrow can increase the hematopoietic activity to compensate for the decreased activity in the irradiated area and regeneration in the field does not occur. When 50–75% of the bone marrow is irradiated, the surrounding unirradiated bone marrow becomes more active and extends to previously inactive areas such as the femur.[12]

Currently, with fractionated radiotherapy regimens and generally smaller volumes, clinically relevant haematotoxicity events can be avoided. A retrospective study found that the most significant predictor was the use of a combination of myelosuppressive chemo-therapy and radiotherapy with a large volume of active bone marrow.[28] Most radiation fields only expose less

than 25% of bone marrow which has the potential to cause chronic myelosuppression. Radiation outside the pelvic field does not provide a significant volume of bone marrow exposure.[35] Widespread bone mets with hemibody irradiation will cause severe hematologic toxicity so other therapies are recommended, eg IV radio isotopes strontium 89, samarium 153, radium 223 which are less toxic.[6]

Hematopoietic Syndrome

The hematopoietic syndrome is generally characterized by the occurrence of thrombocytopenia, granulocytopenia, and lymphocytopenia.[29] Animal studies have shown that hematopoietic stem cells have a D0 of about 0.95 Gy.[33] That is, a dose of 0.95 Gy reduced the stem cell population by up to 37%. For this reason, hematopoietic syndrome is seen with radiation exposures exceeding 1 Gy. At doses below 1 Gy, the surviving proliferative cells (via accelerated proliferation) will be able to replenish the mature functional compartment, and only a clinically insignificant decrease in the blood cell count can be seen.[36] As the absorbed dose increases, more and more hematopoietic stem cells and precursor cells will be killed, and few or no cells will enter the postmitotic compartment. Circulating mature cells that are unaffected by radiation die once they reach their physiological level. The onset of signs and symptoms is dependent on the degree of physiological cellular loss from circulating cells and the reduced dose-dependent supply of mature cells from the depleted proliferative compartment. The balance between these two phenomena results in different degrees of pancytopenia with a predisposition to infection due to leukopenia and bleeding from thrombocytopenia. The severity of signs and symptoms (bone marrow hypoplasia or aplasia) and the likelihood of recovery will depend on the dose absorbed, the rate of dose, and the overall volume of bone marrow irradiated. If there is no regeneration, death usually results from infection and/or bleeding at a dose of 4.5–6 Gy without supportive care.[33]

Lymphopenia due to radiation-induced apoptosis occurs before the onset of other cytopenias. This can be seen within the first 6-24 hours after exposure to moderate or high doses. The rate of lymphocytic depletion and its lowest point is dose-dependent and predictable. This prediction has led to developing a model that uses lymphocyte depletion kinetics as an element of biodosimetry if the absorbed dose is unknown. However, because radiation also interferes with the recirculating properties of lymphocytes, its decrease cannot indicate the extent of stem cell damage.[33,37]

Recent data suggest that immature hematopoietic stem cells are heterogeneous concerning radiation sensitivity. The most immature stem cells responsible for long-term hematopoietic and immune restoration appear to be less sensitive to radiation toxicity than previously thought. The reason for this difference is unknown. Classically, hematopoietic stem cells are defined by their ability to replenish all mature hematopoietic cells and their capacity for extensive self-maintenance and, possibly, self-renewal.[7] While radiation causes bone marrow damage and decreased peripheral blood count, the response of the erythroid and megakaryocyte lineages to irradiation has not been well characterized.[38] Erythroid progenitors and precursors, but not megakaryocyte precursors, are susceptible targets for radiation damage. Restoration of the erythroid lineage depends on the action of erythropoietin on end-stage erythroid progenitors.[39]

Cell depletion in the bone marrow and peripheral blood and the reduction in lymphoid organ weight after irradiation has been widely demonstrated throughout the literature and are dose-dependent on the biologic tissue. A decrease in erythrocytes in the blood after exposure to irradiation causes anemia, usually seen in patients undergoing radiation treatment and chemotherapy. To reduce anemia, blood cell transfusions and erythropoietin can be given to cancer patients.[9]

Hematologic Toxicity

Hematologic toxicity is a relatively severe toxicity that is comparatively common in patients treated with pelvic radiation and chemotherapy. Hematological toxicity places patients at increased risk of infection, fatigue, bleeding, and hospitalization. Patient instability and hospitalization can lead to delays in radiation treatment and missed chemotherapy doses, affecting disease control and survival.[12]

Hematologic toxicity monitored using a peripheral blood count, although this does not immediately reflect damage to the bone marrow due to variations with circulating cell mass, maturation time, and precursor cell radiosensitivity.[40]

Radiotherapy has complex interactions with bone marrow and hematopoiesis, resulting in myelosuppression of all myeloid cell lineages in predictable sequences and timelines. The incidence and severity of bone marrow toxicity during and after radiation is highly dependent on the volume of bone marrow in the radiation field, the dose received by the

bone marrow, the amount of fractionation, and concurrent use of myelosuppressive chemotherapy.

Very low doses of RT (as low as 0.3Gy) can cause measurable changes in peripheral blood counts, especially lymphocytes, due to the radiosensitive nature of these cells. Another source also said that a low dose of radiation, which is 0.25 Gy, can also cause changes in the organs producing the blood. However, due to its ability to repair DNA damage, HSC undergo self renewing proliferation and differentiation to repopulate MPP and HPC which then regenerate mature blood cells to maintain homeostasis of the hemopoietic system.

The long-term effects of radiation on bone marrow at high doses (cumulatively 30 Gy or 20 Gy in a single dose) have been shown to vary according to the percentage of bone marrow in the radiation field. If less than 50% of the bone marrow is irradiated, the surrounding unirradiated bone marrow may increase the hematopoietic activity to compensate for the decreased activity in the irradiated area. Under these circumstances, HSCs can undergo self-renewal proliferation and differentiation and restore hematopoietic homeostasis. However, if the radiation dose received by the bone marrow is too large, it can cause impaired blood cell proliferation through the induction of apoptosis, differentiation, aging, and damage to the HSC niche, which can ultimately lead to bone marrow failure and cell death.

Conclusion

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