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Review Article

Thrombocytopenia in solid malignancies: A review

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ABSTRACT

Thrombocytopenia is one of the most frequent complications associated with cancer or its treatment. Since Radiotherapy and chemotherapy are commonly used for treatment of cancer, Unfortunately, these treatments frequently cause acute and/or long-term bone marrow injury that can adversely affect the quality of life and the course of treatment. There is a need to maintain a safe platelet count to allow effective treatment of the underlying malignancy, prevent bleeding complications and to minimize the use of platelet product transfusion.

1. Introduction

Thrombocytopenia is an extremely common complication of cancer and its management. It is most often found in hematological malignancies yet it is likewise ordinarily experienced in patients suffering from solid tumors as a result of the disease itself or it may be a consequence of treatment. The etiology of thrombocytopenia in cancer patients can be assorted and multifactorial. Systemic chemotherapy frequently causes thrombocytopenia. The degree and duration of thrombocytopenia often depends upon the nature of chemotherapeutic treatment whether myeloablative, as used in stem cell transplants, or non-myeloablative, as typically used in solid non-hematologic malignancies.

The main causes of thrombocytopenia are increased platelet destruction and diminished platelet production. Less frequent are splenic sequestration and dilutional thrombocytopenia.[1] Additional reasons for significant thrombocytopenia include tumor involvement of bone marrow and spleen leading to decreased platelet production and increased platelet destruction; microangiopathic disorders such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Secondary immune thrombocytopenia can also be seen in many lymphoproliferative malignancies and can also be associated with broad differential diagnosis associated with cancer related thrombocytopenia, a careful diagnostic evaluation is indicated.[2]

Bone marrow suppression is the important dose-limiting side effect of chemotherapy and radiotherapy for cancer. Although acute myelosuppression is a prompt concern for patients undergoing cancer therapy, its management has been improved significantly in recent years by the use of various hematopoietic growth factors. However, many patients receiving chemotherapy and/or ionizing radiation also develop residual or long-term bone marrow injury (a sustained decrease in hematopoietic stem cells reserves due to an impairment in hematopoietic stem cells self-renewal) after the recovery from acute myelosuppression. Unlike acute myelosuppression, residual bone marrow injury is latent and long lasting and shows little tendency for

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recovery. Following additional hematopoietic stress such as subsequent cycles of consolidation cancer treatment or autologous bone marrow transplantation, residual bone marrow injury can deteriorate to become a hypoplastic or myelodysplastic syndrome.[3]

2. Thrombocytopenia in Chemotherapy and Radiotherapy

Megakaryopoiesis involves the gradual differentiation of immature megakaryocyte progenitors into diploid megakaryocytes, which undergo a progressive polyploidization and a subsequent process of cytoplasmic maturation leading to platelet release in the bone marrow sinusoids. Besides thrombopoietin, which is the essential growth factor responsible for platelet production, several hematopoietic growth factors such as interleukin (IL)-3, IL-6, IL-11, stromal cell–derived factor 1, and stem cell factor have been shown to influence megakaryopoiesis at different developmental stages.

Myelosuppressive chemotherapy causes various grades of thrombocytopenia, the severity of which depends upon the dose and type of the therapy. Not only the thrombocytopenia confers a risk of bleeding and the magnitude of risk is closely correlated with the severity and duration of thrombocytopenia. The frequency of life threatening hemorrhagic crisis is approximately 5-6% when platelet falls below 20,000-50,000; while it is 10% for platelet count 10,000-20,000; and 20-40% for the count less than 10,000 cells/μl. Thrombocytopenia poses a major dose-limiting hematologic toxicity, especially in the treatment of potentially curable cancers. Either reduction of dose of chemotherapy is advised or delay in the dose delivery is warranted as a preventive measure against chemotherapy-induced thrombocytopenia. This can often lead to poor outcomes, including reduced disease free periods and overall survival.[4]

The majority of chemotherapeutic agents can cause myelosuppression in a dose-dependent manner. Among these compounds, alkylating agents, pyrimidine analogs, anthracyclines, anthraquinones, nitrosoureas, methotrexate, hydroxyurea and mitomycin-C are highly cytotoxic to Bone marrow.[5] The incidence of chemotherapy-induced thrombocytopenia varies greatly depending on the type of treatment intervention, with gemcitabine- and platinum-based regimens having the highest rates. There are different mechanisms that cause decrease in the platelet count like alkylating agents affect stem cells, cyclophosphamide affects later megakaryocyte progenitors, Cyclophosphamide spares hematopoietic stem cells because of their abundant levels of aldehyde dehydrogenase, but affects later megakaryocyte progenitors, bortezomib prevents platelet release from megakaryocytes, and some treatments promote platelet apoptosis.[6] Finally, chemotherapy may enhance platelet clearance by immune mechanisms. In the treatment of many lymphomas, administration of single-agent fludarabine has been noted to produce an immune thrombocytopenia in up to 4.5% of patients.[7] This ITP typically responds to rituximab.[8] Platelet destruction is also increased when chemotherapy drugs produce a drug-dependent secondary immune thrombocytopenia, but this effect is uncommon.

Radiation induced thrombocytopenia is a significant cause of morbidity and mortality.[9] In patients receiving radiation therapy, thrombocytopenia can result in delays of therapy and significant bleeding requiring transfusion of both platelets and packed red blood cells. Additionally, in radiation injured persons, bleeding and thrombocytopenia are directly responsible for significant mortality.[10] Some studies have shown that platelet count correlates better with survival after radiation exposure than white blood cell count.[11] In an era of greater concerns of untoward radiation exposure by the general population, strategies to treat or prevent radiation induced thrombocytopenia have gained additional attention and strategies to easily improve survival are needed.

Acute myelosuppression caused by chemotherapy or ionising radiation occurs due to induction of hematopoietic cell apoptosis.[12] Stem cells differentiate into cells committed to megakaryocyte differentiation (megakaryocyte colony-forming cells) Hematopoietic stem cells are more dormant and more capable in repairing DNA damage, they are more resistant to induction of apoptosis after exposure to IR and chemotherapy than proliferating hematopoietic progenitor cells. Therefore, acute bone marrow injury is primarily caused by damage to hematopoietic progenitor cells.[13]

Hematopoietic stem cells undergo self renewing multiplication to repopulate hematopoietic progenitor cells. Various hematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF), granulocyte/macrophage-colony stimulating factor (GM-CSF), erythropoietin or thrombopoietin have been widely used in clinic to promote the recovery of bone marrow hematopoietic function in patients after cancer therapy.

Unlike acute myelosuppression, residual Bone marrow damage is latent. Patients with residual Bone marrow injury usually have normal blood cell counts under normal homeostatic conditions in spite of a decrease in Hematopoietic stem cells reserves.[14] Because of this latency, the clinical implications of the residual Bone marrow injury have been largely overlooked. Moreover, the importance of long-term Bone marrow damage is further obscured by the seemingly complete recovery of peripheral blood cell counts, bone marrow cellularity and the number of colony-forming units especially after the use of hematopoietic growth factors.[15] In fact, the use of hematopoietic growth factors may worsen

chemotherapy and ionising radiation-induced residual Bone marrow damage by promoting lematopoietic stem cells and hematopoietic precursor cell proliferation and differentiation at the expense of hematopoietic stem cells self-renewal.[16] This could lead to an accelerated exhaustion of hematopoietic stem cells and further compromise the long-term recovery of bone marrow hematopoietic function. Although residual bone marrow damage is latent, it is long lasting and shows little tendency for recovery. It can lead to the development of hypoplastic marrow or a myelodysplastic syndrome at later times or following additional hematopoietic stress such as subsequent cycles of consolidation cancer treatment.[17]

3. Residual Bone Marrow Injury: Refractory Thrombocytopenia

Residual bone marrow injury is best defined by a significant reduction in hematopoietic stem cells reserves resulting from a defect in hematopoietic stem cells self-renewal. Following mechanisms have been proposed to explain how chemotherapy and ionizing radiation impair hematopoietic stem cells self-renewal function and reduce hematopoietic stem cells reserves: (1) quantitative reduction in hematopoietic stem cells due to induction of cell death or apoptosis; (2) qualitative changes in hematopoietic stem cells replicative function resulting from induction of hematopoietic stem cells senescence; and/or (3) damage to Bone marrow stromal cells or hematopoietic stem cells niches that support hematopoietic stem cells self-renewal.[18]

3.1. Induction of hematopoietic stem cell death

Inappropriate and excessive spontaneous and activation-induced apoptosis can lead to myelosuppression and result in myelodysplasia, thrombocytopenia, leukopenia and lymphopenia. The induction of bone marrow hematopoietic cell apoptosis, particularly in the hematopoietic progenitor cells compartment, is largely responsible for chemotherapy- and Ionising radiation-induced acute bone marrow suppression.[19,20] Zeuner et al studied the effects of chemotherapeutic agents on primary megakaryocytes by using a culture system that summarises in-vitro human megakaryopoiesis and the study showed that megakaryocytic progenitors are destroyed at early stages of differentiation by cytotoxic cells.[21–23] The results presented indicated that cytokine stem cell factor is a potent antiapoptotic factor for megakaryoblasts, which are the preferential target of chemotherapeutic drugs among maturing megakaryocytic cells, and therefore may be useful in the prevention of drug-induced thrombocytopenia.

3.2. Induction of hematopoietic stem cells senescence

Cells undergo senescence after extensive replication or exposure to a genotoxic or oncogenic stress.[24] Although senescent cells remain metabolically active, they are no longer capable of dividing and thus are considered as non-functioning cells from a reproductive view. It has been hypothesized that chemotherapy and ionising radiation cause residual bone marrow injury primarily by induction of hematopoietic stem cells senescence which impairs hematopoietic stem cells replication and self-renewal leading to the reduction in hematopoietic stem cells reserves.[25] Impairment in hematopoietic stem cells self-renewal has been well documented in patients and animals after exposure to irradiation or treatment with various chemotherapeutic agents that can cause residual Bone marrow injury. It has been hypothesized that hematopoietic stem cells also have a finite cell replicative ability and can undergo replicative senescence or exhaustion after forced extensive proliferation.

The role of reactive oxygen species in hematopoietic stem cells senescence is studied further which shows that compared to various bone marrow stromal cells and other hematopoietic cells, hematopoietic stem cells are relatively more sensitive to oxidative stress, probably in part because they are present in a hypoxic environment in the hematopoietic stem cells niche and maintain in a quiescent state.[26] Therefore, a moderate increase in Reactive oxygen species is capable of impairing the ability of hematopoietic stem cells to self-renew via induction of hematopoietic stem cells senescence, which can cause premature exhaustion of hematopoietic stem cells and long term bone marrow suppression. Reactive oxygen species can regulate hematopoietic stem cells function in a concentration-dependent manner. Low levels of Reactive oxygen species appear to be required for hematopoietic stem cells proliferation, differentiation, and mobilization. However, increased production of reactive oxygen species can be detrimental to hematopoietic stem cells.[27]

4. Bone Marrow Injury

Damage to bone marrow stroma has been observed after exposure to Ionising radiation or treatment with ionising radiation or chemotherapy.[28] However, compared to hematopoietic stem cells and hematopoietic progenitor cells, bone marrow stroma cells are relatively more resistant to chemotherapy and ionising radiation. In particular, it has been shown that bone marrow cells from normal mice transplanted into BU-treated mice were capable of restoring hematopoietic function to near normal levels, while transplantation of bone marrow cells from BU-treated mice failed to do so. Similar results were also found in bone marrow cells from irradiated animals, which were

unable to engraft as efficiently as un-irradiated cells after transplantation.[29]

5. The role of Thrombopoietin in Platelet Production

Thrombopoietin is usually produced in the liver, lacks a storage form, and is released into the circulation. During circulation, most thrombopoietin is cleared by thrombopoietin receptors on platelets and possibly on bone marrow megakaryocytes. These cells bind, internalize, and then degrade thrombopoietin. The relatively small amount of thrombopoietin present in the circulation controls the basal rate of thrombocyte formation. Thrombocytopenia does not raise the rate of hepatic thrombopoietin production, and no other physiologic stimulus has been proven to affect this rate. Despite a 10- to 20-fold increase in thrombopoietin concentration, hepatic thrombopoietin mRNA levels remain unaltered in severe thrombocytopenia produced by chemotherapy.[30]

The rate of platelet formation is inversely related to circulating thrombopoietin levels. With the reduction in platelet production as a result of chemotherapy, thrombopoietin clearance is reduced and levels rise.[31] There is a log-linear relationship between the rise in thrombopoietin concentration and the fall in the platelet count after chemotherapy.

Thrombopoietin stimulates mitosis of megakaryocyte colony-forming cells. Its major effect in very low concentrations is to increase megakaryocyte endomitosis and increase megakaryocyte ploidy, greatly expanding the megakaryocyte pool. Thrombopoietin then stimulates megakaryocyte maturation.

Two recombinant thrombopoietin molecules were developed after the discovery of thrombopoietin in 1994. The full glycosylated thrombopoietin protein recombinant human thrombopoietin (rhTPO) was generated in Chinese hamster ovary cells. The other, PEG-rhMGDF (pegylated recombinant human megakaryocyte growth and development factor), was a non-glycosylated protein composed mainly of the first 163 amino acids of thrombopoietin conjugated to polyethylene glycol. With half-lives of around 40 hours, both compounds were strong stimulators of platelet formation. Development of both was stopped due to concerns over neutralizing antibody formation against PEG-rhMGDF.[32] Despite the failure of one of these recombinant thrombopoietin molecules, interest turned to developing thrombopoietin receptor agonists with novel properties and less risk of antibody formation.[33]

6. Other Agents

Management approaches to chemotherapy-induced thrombocytopenia are mainly based on platelet transfusions. Over the past decade, several pharmacologic agents with thrombopoietic activity have been evaluated for the supportive therapy of cancer patients including thrombopoietin, IL-3, IL-6, and IL-11. At present, IL-11 is the only cytokine licensed in the United States for the treatment of chemotherapy-induced thrombocytopenia, but it's thrombopoietic activity is modest and its use is often associated with unfavorable side effects.[4,34] Recombinant IL-11 (oprelvekin) has been shown to reduce the need for platelet transfusions from 96% to 70% of patients who had been transfused with platelets in a prior cycle and who then received additional chemotherapy.[35] The primary regulator of megakaryocytopoiesis and thrombopoiesis, thrombopoietin, and its analogues were shown to be the most powerful stimulators of thrombopoiesis in early clinical studies, with few side effects. They've also been proven to improve platelet recovery following chemotherapy, although preliminary results from trials looking at their potential to prevent severe thrombocytopenia associated with leukaemia and bone marrow transplantation have been conflicting.[36] The administration of hematopoietic growth factors after chemotherapy offers a faster recovery from myelosuppression in patients with solid tumors. However, an important goal of anticancer therapies would be to avoid the occurrence of myelosuppression either through more selective therapeutic strategies that target only neoplastic cells or through the use of antiapoptotic factors that specifically protect hematopoietic cells. The results presented in this study indicate that stem cell factor is a potent anti apoptotic factor for megakaryoblasts, which are the preferential target of chemotherapeutic drugs among maturing megakaryocytic cells, and therefore may be useful in the prevention of drug-induced thrombocytopenia.[37]

7. Conclusion

The hematopoietic framework is especially powerless to the toxic effects of anticancer therapy. While actuating apoptosis in cancerous cells, anticancer medications cause an exhaustion of hematopoietic stem and progenitor cells in the bone marrow. Therapy-related anemia, neutropenia and thrombocytopenia often result in treatment delay thereby undermining the outcome of anticancer therapies. Even new targeted therapies, which are intended to destroy the tumor with insignificant harm to bone marrow, frequently have considerable symptoms on normal hematopoietic cells that limit their successful clinical use. Post-chemotherapy administration of hematopoietic cytokines is being used to limit the negative effects of drug-induced hematotoxicity.[38]

However, this approach presents several limitations due to the inability of currently used growth factors to prevent the occurrence of chemotherapy-induced myelosuppression, non-responsiveness of a significant portion of patients and safety concerns linked to adverse effects and potential tumor-promoting activity.

8. Source of Funding

None.

9. Conflict of Interest

None.

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