Fourth Edition

Current CANCER Therapeutics

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CM CURRENT MEDICINE

Developed by Current Medicine, Inc., Philadelphia

CURRENT MEDICINE, INC.
400 Market Street
Suite 700
Philadelphia, PA 19106

DEVELOPMENTAL EDITOR: *Elise M. Paxson*
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The Editors thank Rowena Schwartz, Pharm. D., for pharmaceutical review of the manuscripts.

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inquiry@phl.cursci.com
www.current-science-group.com

ISBN: 1-57340-176-5
ISSN: 1074-2816

Printed in the United States of America by Port City Press.
5 4 3 2 1

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CHAPTER 25: MYELOSUPPRESSION

Michael S. Gordon

Patients receiving chemotherapy or radiation therapy experience certain side effects. Some (*eg,* acute nausea and vomiting) occur acutely and are managed with medications or intravenous fluids designed to counteract these effects. Other side-effects (*eg,* alopecia), although uncomfortable and perhaps damaging in terms of patient self-image, are not dangerous and do resolve at the conclusion of therapy. Among all side effects seen, those associated with the effects of anticancer therapy on the bone marrow (BM) represent a potentially dangerous and even life-threatening circumstance [1]. Because most anticancer treatments affect rapidly dividing cells preferentially, BM is an ideal target for these effects. This is the primary reason that myelosuppression is among the complications most frequently seen.

Temporary damage to BM can result in decreases in all three major strains of peripheral blood, although effects on leukocytes and especially the myeloid series tend to dominate, given that they have the shortest survival of all BM-derived cells (Table 25-1). This results in a drop in the infection-fighting neutrophil series, with an associated increased risk of infection. Although these patients are at increased risk for both bacterial and fungal forms of infection, the former tends to be more commonly seen. Generally, only patients with long-term severely low (absolute neutrophil count < 250 cells/μL) for lengthy periods experience mycotic infections. Bodey *et al.* [2] reviewed the experience at the National Institutes of Health leukemia service, which defined that both the depth and duration of neutropenia play roles in the risk of developing systemic infectious complications. Because in most cases, neutropenia is of a short duration, the average risk of infection with standard chemotherapy is relatively low. Among the remaining lineages, anemia is most often cumulative in nature. A current controversy disputes which level of anemia represents a sufficiently significant drop to warrant intervention with medical therapy even though transfusion therapy continues to be a mainstay of management of this side effect. This complication most often lowers patients' quality of life by fatiguing them. Finally, a small percentage of patients develops clinically significant thrombocytopenia from cancer therapy. The risk of clinically severe bleeding in patients with thrombocytopenia is low and occurs primarily when the platelet count falls to dangerously low levels. Overall, development of myelosuppression as a complication of cancer therapy can be related to a range of variables (Table 25-2); the development of other complications such as disseminated intravascular coagulopathy or other underlying illness can complicate this issue.

PATHOPHYSIOLOGY

Production of blood cells by BM is an orderly process controlled by both positive and negative regulators termed hematopoietic growth factors (HGFs) and cytokines (Table 25-3) [2]. These include both early-acting stem cell factors (primarily interleukins 1, 3, 6, as well as stem cell factors) and the lineage-specific colony-stimulating factors (*eg,* granulocyte colony-stimulating factors [G-CSF], granulocyte-macrophage colony-stimulating factors [GM-CSF], and erythropoietin). These biologic agents control the proliferation, differentiation, and maturation of multipotential precursor cells that can be directed to various lineages based on the relative expression of specific factors in a BM microenvironment. Hematologic lineages are regulated by a series of feedback loops such as that of the renal tubules that control erythropoietin expression in response to hematocrit.

Blood cell production begins with the multipotential stem cell, which has the ability to self replicate and thereby ensure that adequate precursor cells are always available. The exhaustion of this stem cell supply, although theoretical, could lead to severe BM aplasia and hypoproduction of all blood cells. Although BM aplasia as a result of cancer therapy is rare, it generally only happens with the most intensive chemotherapy regimens.

In general, the environment in which the stem cells exist needs to be conducive to their growth and development. Severe fibrosis from diseases, such as the myeloproliferative disorders or chronic changes as a result of radiation therapy, tends to make BM space inhospitable to blood cell production. This therefore can contribute significantly to the development of myelosuppression.

Kinetically, the myelosuppressive effects of cancer therapy tend to be related to what stage of development is damaged by the agent in question. Neutrophils, which usually survive 7 hours in circulation, are most sensitive to treatment effects. Similarly, platelets that last 7 to 10 days are more commonly affected than erythrocytes, which last 120 days in circulation. The progression of hematopoietic development is similar for all lineages taking approximately 7 days to progress from stem cell to committed progenitor and another 7 to 10 days to progress from committed progenitor to mature cell, ready for release into the circulation. It is this latter 7- to 10-day period that can be compressed by the available CSFs to accelerate blood cell production rapidly.

CAUSES

The principal forms of cancer therapy that cause myelosuppression are chemotherapy and radiation therapy. In the case of radiation, the damaging effect is not limited to the hematopoietic compartment, but to the marrow microenvironment itself. Not uncommonly, it can take up to several years for recovery of a previously irradiated area. In

Table 25-1. Categories of Cytopenias

Lineage	Approximate Survival (in Circulation)	Deficiency
Myeloid	7 h	Neutropenia
Erythroid	120 d	Anemia
Megakaryocyte	7–10 d	Thrombocytopenia

Table 25-2. Factors Associated With Myelosuppression

- Therapy
  - Choice of chemotherapy agents and dose-intensity
  - Radiation therapy including total dose and volume radiated
- Bone marrow reserve
  - Patient's age and nutritional status
  - Prior therapy
  - Bone marrow involvement with malignancy or other process
  - Bone marrow involvement with cancer or other process
  - Comorbid conditions such as autoimmune processes
  - Drug-related effects (nonchemotherapy)
  - Infection-related complications (*ie,* disseminated intravascular coagulation)

contrast to these two therapies, biologic therapy (*eg*, immunotherapy) may cause myelosuppression by inducing a peripheral consumptive state related to hypersplenism or some similar mechanism. This former effect most commonly resolves quickly following discontinuation of these agents. In some cases of antibody-directed irradiation (using a monoclonal antibody to target radiation particles), the impact can be more significant.

Chemotherapy

Chemotherapy affects hematologic cells in much the same way it does cancer cells. Chemotherapy drugs can be classified into categories based on mechanism of action. Alkylating agents typically bind to nucleotide bases of DNA and thereby inhibit protein synthesis and replication. This effect is similar to that of the antitumor antibiotics such as doxorubicin or daunorubicin that intercalate into DNA strands, thus preventing DNA synthesis. Vinca alkaloids (vincristine or vinblastine) and the taxanes (paclitaxel and docetaxel) inhibit microtubular synthesis that inhibits spindle formation preventing cells from actively undergoing mitosis. Finally, antimetabolites frequently substitute themselves for purine or pyrimidine nucleotides, thereby blocking DNA or RNA synthesis. These latter agents may also block specific enzymes required for nucleotide synthesis. BM cells take up these chemotherapy drugs in much the same way as cancer cells. Hence, BM, because of its rapidly proliferating state, often tends to be more sensitive to the effects of chemotherapy because unlike cancer cells, these progenitors often lack mechanisms of resistance to the chemotherapy. An outline of cancer chemotherapeutic agents and their relative effects on different lines is shown in Table 25-4. Several agents such as vincristine, low-dose methotrexate, L-asparaginase, and oral cyclophosphamide generally do not cause significant myelosuppression. Conversely, agents such as the nitrosureas and mitomycin-C frequently induce delayed and prolonged myelosuppression because of their relative effects on the stem cell population.

Immunotherapy

Biologic agents can be divided into two specific groups with regard to their effects on the hematologic system. The first group, which includes the interferons (alfa, beta, and gamma), can exert a direct suppressive effect on BM and although not specifically myelotoxic, certainly is not myelosuppressive. This impact on blood counts is typically relatively rapidly reversible after the drug has been discontinued. In contrast, lymphopenia and neutropenia associated with interleukin-2 (IL-2) appear to be predominantly related to peripheral consumption by immunostimulated cells or by vascular margination of pools of cells. Both these side effects are rapidly reversible, appear to be dose related, and generally are not associated with infectious complications. In addition to the IL-2–mediated neutropenia, this agent has the ability to induce neutrophil dysfunction, which lasts longer than quantitative neutropenia and may be associated with increased infectious risk.

Radiation Therapy

Radiation therapy induces cell death by causing lethal double-stranded DNA breaks. These DNA breaks result in cell death and apoptosis when the cell enters the cell cycle. For this reason, it is cells in G_0 that tend to be more sensitive to DNA damage than those in G_1 or S-phase, which tend to be more resistant due to their ability to correct damage enzymatically. Hence, myelosuppression associated with radiation therapy is often related to the volume of BM irradiated, the total radiation dose, and the patient's overall BM reserve (which may be compromised by either prior therapy or BM involvement with cancer).

DIAGNOSIS

The first evidence of myelosuppression is often a defined drop in the number of peripherally circulating blood cells. Because of the kinetics and life span of blood cells as previously noted, leukopenia and neutropenia are typically the first deficiencies noted. This drop, which may be mild, is frequently found 7 to 10 days following the completion of therapy, although more intensive treatments may accelerate the process. In the case of moderately to severely intensive regimens, thrombocytopenia may be noted at or around the same time. Anemia, as a side-effect of therapy, is more commonly cumulative and develops over time or a series of cycles.

In typical situations, response to the development of cytopenias is an increase in BM production of blood cells. This generally corrects mild leukopenia or thrombocytopenia in a short time (7 to 14 days). In some cases, in which more severe or prolonged myelosuppression occurs, further investigation may be necessary.

Table 25-3. Hematopoietic Growth Factors and Cytokines

	Name	Lineage	Approval Status
Colony-stimulating factors	G-CSF	m	Approved
	GM-CSF	m, mo	Approved
	EPO	e	Approved
	TPO	p	Investigational
	M-CSF	mo	No longer under study
Interleukins	Interleukin-11	p	Approved
	Interleukin-3	m, e, p	No longer under study
	Interleukin-6	p	No longer under study
	Interleukin-1	m, e, p	No longer under study

e—erythroid; G-CSF—granulocyte colony-stimulating factor; GM-CSF— granulocyte–macrophage colony-stimulating factor; EPO—erythropoietin; m—myeloid; mo—monocytic; M-CSF—macrophage colony-stimulating factor; p—platelet; TPO—thrombopoietin.

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