



Hematology and Associated Laboratory Tests

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Introduction

Hematologic toxicity is a major dose-limiting side effect of cytotoxic cancer drugs and some other targeted cancer drug therapy (e.g., palbociclib). Since bone marrow cells proliferate continuously and cytotoxic cancer drugs have their greatest effect on rapidly growing cells, suppression of bone marrow activity (myelosuppression) is prevalent. Myelosuppression is the most common cause of treatment delays and dose reductions in cancer patients receiving cancer drug treatment. Myeloid stem cells are the precursors to neutrophils, monocytes, platelets, and red blood cells; therefore, myelosuppression leads to a reduction in the number of white blood cells (WBCs), platelets, and red blood cells (RBCs).

Each cancer drug or combination of drugs affects the production and growth of the different blood cell types to varying degrees and in varying ways. This in turn produces a characteristic degree of toxicity at a predictable time following drug administration. Some drugs will cause little or no hematologic toxicity, while others will produce a more definitive and predictable dose-related myelosuppression. Therefore, understanding the pharmacokinetic and pharmacologic profile of cytotoxic agents helps in the identification of myelosuppressive patterns.

Nadir is a term commonly used when discussing myelosuppression. The nadir occurs at the time following drug administration when the lowest cell counts are observed. Following the administration of cytotoxic cancer drugs, the neutrophil and platelet nadirs occur after approximately 7-14 days and reflect the maturation cycle of the cells: 8-10 days for neutrophils and 7–10 days for platelets.

Recovery is another commonly used term when discussing myelosuppression. Recovery occurs when the cell numbers return from the nadir to normal or near normal levels. Many BC Cancer protocols have a duration of 21 to 28 days, which allows for recovery from nadir for most cancer drugs. Some protocols have longer durations, to allow for the delayed nadirs and prolonged recovery times that occur with certain cancer drug agents. For example, lomustine is given as a single dose orally every six weeks for recurrent malignant brain tumours in the CNCCNU protocol. Agents that affect hematopoietic stem cells (e.g., carboplatin) can also produce a late nadir. The dose interval for some carboplatin-containing protocols (e.g., GOOVCAD) may be increased if hematologic recovery is delayed.

Hematological toxicity may be more pronounced in patients who have had prior radiation therapy. Other patient-specific factors such as age, nutritional status, prior cancer drug treatment and bone marrow reserve also play a role in the degree and

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severity of toxicity experienced by patients receiving cancer drug treatment.

Numerous strategies have been developed to help reduce or prevent bone marrow toxicities and potential life-threatening complications:

- Select less myelosuppressive drugs or therapies when multiple equally effective options exist
- Consider dose reductions
- Administer biologic response modifiers (e.g., filgrastim) to increase blood cell counts
- Use prophylactic antibiotics to prevent the development of an infection when the patient's white blood cell count is expected to be low
- Consider blood or platelet transfusions

Close monitoring for suppression of neutrophils (neutropenia), platelets (thrombocytopenia), and red blood cells (anemia), in conjunction with the prevention and treatment of these toxicities, plays an important role in the management of cancer patients on drug therapy.

The complete blood count (CBC) is a commonly ordered clinical laboratory test for oncology patients. A CBC measures white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), mean cell volume (MCV), red cell distribution (RDW), and platelet count. A CBC can also be ordered with differentials, which will analyze the various types of WBCs – neutrophils, lymphocytes, monocytes, eosinophils and basophils. Some laboratories may also include band neutrophils in the WBC differential.

See the *Lab Test Interpretation Table*, located below this document on the [Clinical Pharmacy Guide](#) webpage, for examples of normal values and for interpretation tips.

Neutrophils

The terms polymorphonuclear leukocytes ("PMNs" or "polys"), segmented neutrophils ("segs") and granulocytes ("grans") are commonly used in clinical practice to describe neutrophils. Although the terms granulocyte and neutrophil are not entirely equivalent (granulocytes are comprised of neutrophils, eosinophils, basophils and monocytes), the two are commonly interchanged since granulocytes are almost entirely (approximately 95%) comprised of neutrophils. Due to their short life span (9-10 days) and rapid

proliferation, neutrophils are particularly vulnerable to the toxic effects of cytotoxic drugs. Mature neutrophils (also called “polys” or “segs”) constitute approximately 50 – 70% of circulating WBCs, while immature neutrophils (also called “bands”, “band cells” or “stabs”) constitute another 3 – 5%. The term “left shift” is sometimes used to describe an increase in the number of immature neutrophil count.

The absolute neutrophil count (ANC) is a measurement of the total number of circulating neutrophils. A normal ANC is between $2 - 7.5 \times 10^9$ neutrophils/L of blood and can be measured directly as part of the WBC differential. Alternatively, it can be calculated by multiplying the total WBC count by the percentage of mature and immature neutrophils (i.e., polys + bands). The usual pattern of suppression followed by recovery resembles that of a valley: the depth represents the nadir, and the width shows the timeline over which suppression and recovery occurs. The severity and duration of neutrophil suppression is related to the dose, pharmacokinetic properties, and administration schedule of the drug(s). Daily drug administration over several days generally produces nadirs that are longer in duration and less pronounced; drug administration as a single dose generally produces nadirs that are shorter in duration but with more pronounced suppression.

Neutropenia

On occasion, the ANC may not fully recover to acceptable levels by the beginning of the next cycle of cancer drug treatment. In this case, the dose is often reduced or delayed. In several BC Cancer protocols, action is required when the ANC is less than 1.5×10^9 neutrophils/L; however, in many other protocols, this threshold is even lower. It is extremely important that the correct protocol is reviewed when determining cancer drug doses and possible dose reductions based on ANC.

When the ANC falls below 1.5×10^9 neutrophils/L, the patient is at greater risk for developing an infection. The degree of risk for infection is directly related to the severity and duration of neutropenia. When neutropenia occurs during cancer drug treatment, doses may be delayed, and/or reduced and/or patients should be closely monitored in subsequent cycles in order to decrease the risk of further neutropenia. Depending on the protocol (e.g., BRAJACTG), some patients may require filgrastim (i.e., G-CSF) to decrease the risk of neutropenia.

The usual signs of infection are often absent in neutropenic patients. Because the WBC count is inherently low in these patients, the rise in WBC count that is the usual marker of infection does not occur. Therefore, the most reliable indicator of an infection is the

presence of fever. Diagnosis can be confirmed with a culture. When “febrile neutropenia” is diagnosed, the infection may be potentially life threatening; therefore, prompt initiation of empiric antibiotic therapy is required, because the possibility of infection cannot be excluded.

Platelets

Platelets, also known as thrombocytes, are blood cells that are also sensitive to the myelosuppressive effects of cancer drugs but generally exhibit a lesser degree of toxicity than white blood cells. A normal circulating platelet count is between $150 - 400 \times 10^9$ platelets/L of blood. Because platelets are involved in the process of coagulation, risk of bruising and bleeding increases when counts fall below the normal range.

Thrombocytopenia

In cases where the platelet counts have not fully recovered by the beginning of the next cycle of cancer drug treatment, a reduction in cancer drug dose(s) and/or a delay in treatment may be required. The majority of BC Cancer protocols require the platelet count to be at least 100×10^9 platelets/L for the patient to receive full doses of cancer drugs. It is important that the correct protocol is reviewed when determining dose reductions or treatment delays based on platelet counts. While thrombocytopenia in the cancer patient may be a result of bone marrow infiltration by malignant cells or radiation therapy, the most common cause is cancer drug treatment.

Red Blood Cells

Red blood cells (RBCs), or erythrocytes, are least affected by myelosuppressive cancer drugs because their average circulating life span is considerably longer than that of neutrophils or platelets (approximately 120 days). However, anemia risk is cumulative, increasing with increased cancer drug treatment cycles. Symptoms may include fatigue and weakness. A common anemia-inducing cancer drug is CISplatin. As with thrombocytopenia, anemia is not solely caused by myelosuppressive cancer drug treatment. Other contributing factors include chronic disease, chronic blood loss, inadequate nutrition, tumour invasion into the bone marrow, prior cancer drug treatment, and radiation therapy.

Other Hematologic Toxicities

Other hematologic toxicities may occur as a result of cancer drug treatment. While these toxicities do not generally result in dose modifications, they may necessitate treatment delays and discontinuation or change in cancer drugs. For example, patients receiving gemcitabine in combination with cisplatin (as in the [LUAVPG](#) protocol) may be at risk for developing hemolytic uremic syndrome and irreversible renal failure if there is pre-existing renal dysfunction.

It is important to be aware of any potential toxicity that may occur as a result of a specific BC Cancer treatment protocol. A thorough review of patient-specific factors will identify these toxicities and provide guidance on how to deal with them. This information is found at the end of the protocol summary under Precautions, and in the individual drug monograph of the [Cancer Drug Manual](#). The dose modification information found in the BC Cancer protocols is disease, treatment and drug combination specific, and takes precedence over the more generalized dose modification information found in the CDM drug monographs.