Adverse Haematological Complications of Anticancer Drugs
Clinical Presentation, Management and Avoidance

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Summary

Haematological complications frequently occur in patients treated with chemotherapeutic agents. The degree and duration of bone marrow suppression depends upon the type of agent used. In general, agents that are cell cycle phase-specific tend to cause early myelosuppression with rapid marrow recovery, as compared to the non-phase-specific agents. Host factors including patient age, nutritional status, marrow infiltration or damage, and hepatic and renal function also affect haemotoxicity.

Chemotherapeutic agents suppress proliferating or potentially proliferating precursors of neutrophils, platelets and red blood cells to the same extent. With most drugs, neutropenia tends to be dose limiting and more severe than thrombocytopenia. Because of the longer life span of red blood cells, severe anaemia is rarely a problem.

The management of myelosuppression is multifaceted, and consists of aggressive antibiotic therapy to treat or prevent the infections that occur with neutropenia, as well as red blood cell
and platelet transfusion support to correct anaemia and prevent bleeding. The role of the haemo­
poietic growth factors including erythropoietin, colony-stimulating factors and the interleukins
is currently being evaluated in clinical trials.

Haemolytic uraemic syndrome, haemolytic anaemia and therapy-induced myelodysplasia and/
or acute leukaemia are uncommon and potentially severe complications of chemotherapeutic
agents.

1. General Considerations

Although there had been interest, intrigue and charlatanism in using various systemic and topical
compounds in the treatment of cancer for several thousand years, the age of successful chemotherapy
had its beginning in 1943 when a patient with Hodgkin's disease was treated with nitrogen mus­
tard. Interest in mustard compounds began after World War I, based on the observation that sol­
diers exposed to sulphur mustard gas suffered from leucopenia. Nitrogen mustard (chlormethine; me­
chlorethamine) was the first useful compound synthesised in this family. At the same time, the la­
borious task of determining which of the approximately 200 000 known chemicals possessed chemotherapeutic properties was undertaken. Chemicals with similar structural properties were
grouped together and studies were done to determine their effect on tumours in animals and cell
cultures. Effective drugs were identified and clinical studies followed (Pack & Ariel 1968).

New drugs continue to be developed on an annual basis. Improvements in survival rates for many
malignancies, in particular the haematological malignancies and germ cell tumours, are due to the
development of these new drugs and to the use of drug combinations. As these drugs, which are gen­
erally not tumour-specific, are more widely used and doses are escalated, more unwanted and un­
expected complications are identified.

To produce an antineoplastic response, a drug
must be present at the tumour site in an adequate
concentration. The concentration will depend upon
drug absorption and distribution to the site of dis­
ease via the blood stream. Well perfused organs
initially receive the bulk of the drug after absorp­
tion. Once absorbed, chemotherapeutic drugs may
be metabolised to active by-products or inactive
constituents that are ultimately excreted. The liver
serves as a common site of such biotransforma­
tion. Excretion occurs predominantly through the
liver or kidney. In this review, normal renal and
hepatic function is assumed.

There are significant differences between the
toxic effects of the chemotherapeutic agents. These
may be dose-dependent or idiosyncratic. However,
it is the dose-dependent effect of these drugs on the
normal haemopoietic system and the subsequent
manifestations in the peripheral blood cell counts
that constitute the major haematological toxicity.

With the exception of the lymphocyte, no direct
effect is observed on the mature cells in the blood
or the bone marrow. It is the proliferating or the
potentially proliferating pool of neutrophil, platelet
and red blood cell precursors that is affected. The
life span of peripheral blood cells determines the
rate at which a particular cytopenia develops. Neu­
traphils survive for about 10 hours, platelets for
about 10 days, and red blood cells for about 120
days. Thus, in the absence of production, neutro­
penia rapidly occurs once the storage pool of neu­
traphils is exhausted. Thrombocytopenia gradually
develops over 7 to 10 days. However, anaemia de­
velops much more slowly because of the long life­
span of the red blood cells.

1.1 Cell Cycle Activity

The haemopoietic stem cell gives rise to the 3
cell types mentioned above. In addition, there are
populations of committed precursors which are ac­
tively cycling to produce the mature cells which are
seen in the peripheral blood. The effect of a drug
depends on its site of action in the cell cycle. Nor­
mal cells divide in a predictable fashion. Four