PRACTICAL DRUG SAFETY

Drug Safety 2003; 26 (10): 691-706
0114-5916/03/0010-0691/$30.00/0

Drug-Induced Myelosuppression
Diagnosis and Management

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Contents

Abstract

Myelosuppression is a common and anticipated adverse effect of cytotoxic chemotherapy. It is a potential but rare idiosyncratic effect with any other drug, but there is a recognised association with a number of higher-risk agents which justify additional vigilance. Genetic risk factors are being identified which may

predispose individuals to this reaction with particular drugs. As marker tests become available, dose adjustment or alternative treatment choices may help to avoid more severe reactions. Myelosuppression is potentially life threatening because of the infection and bleeding complications of neutropenia and thrombocytopenia. Strategies for monitoring, early detection, diagnostic confirmation and appropriate supportive care are well developed for cytotoxic therapy. Developments in antimicrobial chemotherapy, blood product transfusion support and growth factor therapy have improved outcomes. These advances are largely applicable to idiosyncratic drug-induced myelosuppression, reinforcing the importance of early recognition and referral to appropriate expertise. Many reactions will resolve on drug withdrawal with appropriate supportive care during the period of cytopenia. Prolonged marrow failure may require more specific treatment with intensive immunosuppression or consideration of bone marrow transplantation.

By far the commonest cause of combined peripheral blood cytopenias in the industrialised world today is myelosuppression occurring as an adverse effect of cytotoxic chemotherapy for neoplastic disease. Drugs in this category typically produce predictable dose-dependent myelosuppression, which is reversible at therapeutic doses. These are type A reactions according to the classification of Rawlins and Thompson.[1] Such agents are generally prescribed by doctors with expertise and facilities for the monitoring, management and supportive care of these anticipated effects. Myelosuppression is the principal dose-limiting effect for most cytotoxic agents, but in the treatment of malignant disease it is often appropriate to accept a narrow therapeutic index for effective treatment. Advances in supportive care with antimicrobial, blood product, growth factor and stem-cell rescue strategies have enabled an acceptable intensification of many regimens, with resulting therapeutic advances in the management of malignant disease.

Much less common, but more worrying for the general prescriber, and therefore more important for consideration here, is the unpredictable, idiosyncratic (type B)[1] occurrence of myelosuppression unexpectedly related to other drug treatment. The resulting peripheral blood cytopenias, particularly neutropenia and thrombocytopenia, are potentially life threatening. However, the principles and advances in supportive care and management in this situation are the same as for cytotoxic induced myelosuppression. Early recognition and referral for care by practitioners with appropriate expertise and facilities is therefore important.

This article will review the normal haemopoietic function of the marrow, the mechanisms by which drugs may cause myelosuppression, and the categorisation of the resulting clinical syndromes. Examples of individual drugs with important associations with myelosuppression are given. Practical strategies for prompt recognition, diagnosis, management and prevention are then discussed.

Myelosuppression manifests as peripheral blood cytopenia(s) – anaemia, leucopenia, thrombocytopenia. Drugs often cause peripheral cytopenias by shortening peripheral blood cell survival rather than by suppressing marrow cell production, e.g. autoimmune haemolytic anaemia and immune thrombocytopenia. These conditions will not be covered.

1. Normal Bone Marrow Haemopoeitic Function

Circulating peripheral blood cells have a limited life span. The principal function of the bone marrow is the continuous replenishment of these mature cells. In an average-sized adult some 3.5kg of vascular marrow tissue distributed throughout the axial skeleton produces some 2.5×10^9 red cells, 2.5×10^9 platelets and 1.0×10^9 neutrophils daily.[2] This highly mitotic activity is capable of considerable

fluctuation according to demand. *In vitro* cell culture studies have elucidated the understanding of the growth, differentiation and maturation of marrow cells, from the self renewing pool of pluripotential stem cells to the mature cells which pass into the peripheral circulation.[3] Control mechanisms include a family of glycoprotein growth factors, several of which, including epoetin (human recombinant erythropoietin), granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), are now synthesisable in commercial quantities and available for therapeutic use.[4]

2. Mechanisms of Drug-Induced Myelosuppression

Myelosuppression by drugs may occur via mechanisms which reduce the cellularity of the marrow (hypoplasia or aplasia, depending on severity), or by interfering with marrow cell maturation without reducing cellularity as in megaloblastic or sideroblastic anaemia. Hypoplasia/aplasia may affect all cell lines, as in aplastic anaemia, or may be selective, e.g. pure red cell aplasia and granulocytic hypoplasia.

2.1 Cytotoxic Drugs

Malignant disease is characterised by uncontrolled cell proliferation, and most cytotoxic drugs interfere with DNA synthesis or produce chemical damage to DNA that interferes with its replication. Others attack the mitotic spindle, inhibit protein synthesis, or induce cell differentiation.[5] Therapeutic efficacy relies on the fact that tumour cells fail to block the entry of damaged cells into the cycle of DNA synthesis and mitosis, which would otherwise allow repair.[6] Normal cells recover, but it is not surprising that dose-limiting toxicity is seen in the marrow that contains the most mitotically active normal cells in the body.

A rare indirect cause of drug-induced myelosuppression is the late development of myelodysplasia or leukaemia as a result of genetic damage from previous exposure to cytotoxic and other drugs,[7] but this is not considered further here.

2.2 Other Drugs: Evidence for Immune Mechanisms

Noncytotoxic drug effects causing acquired marrow failure are more difficult to establish. Theoretical mechanisms include induction of defects in the haemopoietic stem cells, damage to the stromal microenvironment of the marrow, inhibition of the production or release of haemopoietic growth factors or induction of humoral or cellular immunosuppression of marrow cells.[8] Cell culture studies[9] and the therapeutic effect of immunosuppressive therapy[10,11] in some cases of drug-induced aplastic anaemia suggest that T-cell mediated suppressor cell activity plays an important aetiological role in many cases. Evidence of response to plasmapheresis[12] and inhibition of *in vitro* bone marrow growth in culture[13] further support the operation of immune mechanisms.

2.3 Constitutional Risk Factors

Susceptibility to type A reactions varies between individuals because of differences in absorption and metabolism of the drug (pharmacokinetic changes), or differences in target organ sensitivity[14] Some apparently idiosyncratic type B reactions may actually become more appropriately classified as predictable type A reactions for particular individuals with constitutional risk factors, once mechanisms are elucidated and tests to identify those at risk become available.

The antibiotic chloramphenicol was one of the first drugs for which epidemiological evidence indicated a causal association with apparently idiosyncratic aplastic anaemia.[15] An early report of the coincidence of this very rare reaction in a pair of identical twins suggested the possibility of genetic susceptibility.[16]

Associations of particular phenotypes of the human leucocyte antigen (HLA) system with aplastic anaemia (whether or not drug associated) have suggested genetic susceptibility.[17,18]

The antipsychotic agent clozapine has an epidemiologically established association with agranulocytosis.[19] Several series have noted an apparently increased risk of this complication correlated with

HLA phenotype.[20-22] Analysis of a cohort of patients from the Long Island Jewish Medical Centre in New York[23] found that the HLA-B38 phenotype had an incidence of 83% in patients with agranulocytosis, and 20% in clozapine-treated patients who did not develop the complication. The B38 phenotype was part of a haplotype more common in the Askenazi Jewish population, and subsequent work identified two different haplotype associations with clozapine-induced agranulocytosis, one in Askenazi Jewish patients, and one in non-Jewish patients.[24] The association of both haplotypes with variants of the heat shock protein HSP-70, encoded by loci within the MHC region suggests linkage rather than direct association of the HLA in genetic susceptibility.[25]

Mercaptopurine is a thiopurine used extensively in the treatment of childhood acute lymphoblastic leukaemia. Azathioprine is a prodrug of mercaptopurine in widespread use as an immunosuppressive agent in a variety of autoimmune conditions. Mercaptopurine is inactivated by the enzyme thiopurine methyltransferase (TPMT). Genetically determined variations in TPMT activity were found to be associated with occasional unexpectedly severe myelosuppression associated with mercaptopurine[26] and azathioprine.[27] Determination of TPMT activity, either by measurement of enzyme activity or by molecular detection of the polymorphisms associated with reduced activity is feasible and could allow avoidance of drug in deficient patients and logical dose stratification in heterozygotes.[28] A pharmacoeconomic case has been made for this approach prior to the use of azathioprine in dermatological practice.[29] Polymerase chain reaction-based techniques for relevant genotypic analysis offer an attractive alternative to the performance of radiochemical activity assays in pharmacogenetic screening.[30]

Methotrexate is a dihydrofolate reductase inhibitor used extensively as a cytotoxic agent in lymphoid and other malignancies, and as an immunosuppressive agent particularly in inflammatory arthritis. Polymorphisms in the methylenetetrahydrofolate (MTHFR) gene have been associated with variation in efficacy and toxicity of methotrexate in rheumatoid arthritis patients.[31]

There are several other examples of genetically determined variations in enzyme activity, which may predispose individuals to apparently idiosyncratic adverse drug reactions. Variations in cytochrome P450 (CYP) metabolism divide the population into ultra-rapid, normal, intermediate and poor metabolisers of several drugs, and first elucidated with the antihypertensive debrisoquine. Polymorphisms in the gene encoding for the enzyme CYP2D6 identify these phenotypes.[32] Particular genotype/phenotype combinations have been found to be associated with explicable variations in plasma levels, therapeutic and adverse effects with a number of agents. A study in the UK looked at CYP2D6 polymorphism in a series of patients with acquired aplastic anaemia.[33] No specific association was identified, but the study did not have sufficient power to exclude one.

These examples suggest that technologies for predicting the risk of previously apparently completely idiosyncratic reactions may become available for at least some drugs which may help to reduce the incidence of these dangerous complications.

3. Drugs Associated with Idiosyncratic (Type B) Myelosuppression

Whilst most cytotoxic drugs will cause dose-dependent myelosuppression, idiosyncratic reactions are fortunately rare. Possible associations with myelosuppression have been reported for very many drugs. There are no definitive tests to prove an aetiological link in individual cases. Culture studies or detection of drug antibody can occasionally be suggestive, but are not routinely available. Recurrence on deliberate or inadvertent rechallenge provides the strongest evidence but cannot be recommended. Difficulty often arises in the assessment of possible drug causes because there may be a delay between exposure to a causative agent and the subsequent development of cytopenia. The onset of symptoms may then be relatively insidious, and by the time the patient is found to be cytopenic the drug

Table I. Some classes and individual examples of drugs associated with idiosyncratic (type B) myelosuppression[34-39]

Antimicrobials	Chloramphenicol, cotrimoxazole (trimethoprim-sulfamethoxazole), sulfonamides, nitrofurantoin, zidovudine, quinacrine, amodiaquine, mepacrine, pyrimethamine, chloroquine, mebendazole
Antirheumatics	Gold, penicillamine, indomethacin, oxyphenbutazone, phenylbutazone, piroxicam, sulfasalazine, diclofenac, sulindac, allopurinol
Antithyroid drugs	Carbimazole, thiamazole (methimazole), thiouracils
Anticonvulsants	Phenytoin, carbamazepine, felbamate
Psychotropic agents	Phenothiazines, dothiepin, mianserin, clozapine
Cardiovascular drugs	Methyldopa, captopril, lisinopril, ticlopidine
Other drugs	Tolbutamide, acetazolamide, interferon-α

history may be complicated by the use of a number of additional irrelevant agents prescribed for the treatment of the nonspecific presenting symptoms. Robust evidence for causative associations can therefore only come from epidemiological data which reach statistical significance. Causative links in individual cases can only be presumed.

There is considerable overlap between the lists of drugs associated with the different categories of myelosuppression (see section 4), and rather than grouping them separately, important examples are gathered in table I.

4. Categories of Drug-Induced Myelosuppression

4.1 Aplastic Anaemia

Aplastic anaemia is characterised by the occurrence of peripheral blood pancytopenia in the context of reduced or virtually absent haemopoietic cellularity in the marrow, which is replaced by fat cells.

4.1.1 Type A, Dose Dependent (Cytotoxic Drugs)

Many cytotoxic drugs are used in dose schedules that accept temporary moderate marrow hypoplasia as a manageable adverse effect. Occasionally, repeated courses of alkylating agents (in particular busulphan) produce unexpectedly prolonged aplasia. This needs to be distinguished from hypoplastic myelodysplastic progression of the underlying disease for which the drug was being prescribed (busulphan is frequently used in primary myeloproliferative disorders), but is reproducible in a murine model.[40]

4.1.2 Type B, Idiosyncratic

The onset is often more insidious than with cytotoxic myelosuppression and may occur up to several months after drug exposure. Some examples from table I are now considered in more detail.

Quinacrine

This antimalarial was perhaps the first drug for which a robust statistical association with aplastic anaemia was established.[41] It was widely administered as prophylaxis to US troops in malarial areas from 1943–1944, and an incidence of aplastic anaemia of 7–28 cases per 100 000 per year was compared with 1–2 cases per 100 000 in personnel stationed in non-malarial areas not receiving the drug. A characteristic skin rash often preceded the haematological complication.

Chloramphenicol

This broad-spectrum antibiotic was introduced in 1948. Even before its clinical use, the theoretical possibility of haematological toxicity had been raised because of its chemical similarity to the antipyretic amidopyrone which has an association with neutropenia.[42] Reversible changes affecting haemopoiesis are relatively common with prolonged use of the drug and may be due to mitochondrial effects principally altering iron metabolism.[43] Case reports and subsequent epidemiological studies established a causative link with apparently idiosyncratic aplastic anaemia,[15,44,45] the occurrence of which is not related to the dose or duration of drug exposure. Chloramphenicol is also used topically for the treatment of conjunctival infection and there is controversy about whether or not chloramphenicol eye drops may cause aplastic anaemia.[46] Cases of aplastic anaemia in patients receiving chloramphen-

icol eye drops have been reported, but the incidence of aplastic anaemia does not appear to be above the background level to be expected in the absence of any drug exposure. A recent study in the UK, where chloramphenicol eye drops are still widely prescribed, failed to demonstrate detectable serum levels of chloramphenicol after 1–2 weeks of topical ocular treatment.[47] The authors felt that this was theoretical evidence against a potential mechanism for toxicity with this route of administration, which together with the absence of epidemiological evidence failed to support calls for the abolition of topical chloramphenicol use.

Gold and Penicillamine

Aplastic anaemia is a rare complication with these second-line agents for the treatment of inflammatory arthritis. Neutropenia and/or thrombocytopenia often precede the development of aplastic anaemia and regular monitoring allows cessation of drug before this complication arises.[48]

4.2 Selective Marrow Hypoplasia

4.2.1 Pure Red Cell Aplasia

This is characterised by isolated anaemia and reticulocytopenia and the absence of nucleated red cell precursors in an otherwise normal marrow. This reaction is rare, but there is overlap with aplastic anaemia as with agranulocytosis in the implicated causative agents.[49] There are recent reports of emerging associations with the biological response modifier drugs epoetin[50] and interferon-α.[51] Serum from all 13 of a series of patients treated with epoetin for renal anaemia who developed this complication was found to contain neutralising antibodies which inhibited erythroid colony formation in normal marrow, and which bound to conformational epitopes of the epoetin molecule.[50] Supportive care with red cell transfusion is more straightforward as there is no cause for infective or haemostatic complications.

4.2.2 Drug-Induced Neutropenia/Agranulocytosis

Neutropenia is defined by the lower limit of the reference range, which will vary between laboratories but becomes progressively significant in terms of infection risk below 1.5×10^9/L. Agranulocytosis refers to severe neutropenia $<0.5 \times 10^9$/L. In the terminology of adverse drug reactions, agranulocytosis is generally used to describe a rapidly developing severe neutropenia, sometimes with single-dose or short-term exposure in a patient who has taken the drug before,[52,53] whereas drug-induced neutropenia is used to describe a more slowly developing cytopenia with prolonged exposure.[54] The principal mechanism in drug-induced agranulocytosis is immune, and a degree of peripheral neutrophil destruction is involved,[55] but marrow effects merit its consideration with causes of myelosuppression.[56] The cellularity of the marrow, and the degree of representation of early myeloid cells may help to predict recovery time[57] and response to CSF therapy.[58] Drug-induced neutropenia may involve directly marrow toxic as well as immune mechanisms.[59,60]

There is considerable overlap with drugs implicated in the aetiology of idiosyncratic aplastic anaemia. Some drugs merit further individual consideration.

Clozapine

This antipsychotic agent clozapine was introduced in the late 1960s as an effective therapy for schizophrenia without the extrapyramidal adverse effects associated with other major tranquillisers. In Finland in 1975, 16 patients taking clozapine developed neutropenia, an estimated incidence of 2%.[19] Half of them died of infective complications. Because of its unique therapeutic advantages, the drug was not withdrawn, but mechanisms for ensuring careful monitoring were established,[61] as described in section 8.2. Large epidemiological studies[20,62] have subsequently confirmed an incidence of approximately 1% for this complication and have helped to identify potential risk factors, as described above. The aetiology appears to be toxic rather than immune.[63]

Antithyroid Drugs

Propylthiouracil, carbimazole and thiamazole (methimazole) [the active ingredient to which carbimazole is metabolised] are associated with an incidence of agranulocytosis of 3/100 000 per

year.[36] The highest incidence is in the first 3 months of treatment, perhaps as susceptible individuals identify themselves.[64]

Sulfasalazine

Agranulocytosis was found to have an incidence of 1 in 700 patients within the first 3 months of sulfasalazine treatment, following which the risk was low.[65]

4.2.3 Megaloblastic Anaemia

This is defined by a characteristic pattern of morphological abnormalities seen at marrow microscopy, principally affecting the red cell precursors. It reflects impaired nucleic acid synthesis and most commonly occurs as a result of deficiencies of vitamin B12 or folic acid. Anaemia with macrocytosis is the usual peripheral blood manifestation, but neutropenia and thrombocytopenia may also occur. Drugs that interfere with vitamin B12/folic acid metabolism or nucleic acid synthesis may produce the same picture.[66] Examples include the dihydrofolate reductase inhibitors methotrexate and trimethoprim; drugs that affect folic acid absorption/utilisation such as phenytoin; agents that directly affect DNA synthesis including azathioprine, hydroxyurea (hydroxycarbamide), fluorouracil, cytarabine and zidovudine. Administration of folinic acid may reverse these effects except when DNA synthesis is affected directly.

4.2.4 Sideroblastic Anaemia

This is also defined by a characteristic pattern of morphological marrow abnormality, with the accumulation of perinuclear siderotic granules in the mitochondria of nucleated red cells, producing 'ring sideroblasts'. This reflects disordered haem synthesis. This has been reported with the antituberculous agents isoniazid and pyridoxine, as well as with alcohol, chloramphenicol, cycloserine, penicillamine and phenacetin.[67] Deficiency of pyridoxine (vitamin B6) will exacerbate this and supplementation is often used with antituberculous therapy. The oxazolidinone antibiotic linezolid has been associated with cytopenias due to myelosuppression,[68] sometimes associated with sideroblastic change.[69]

5. Diagnosis of Drug-Induced Myelosuppression

The first step in the diagnosis of drug-induced myelosuppression is the recognition and confirmation of the consequent peripheral blood cytopenia(s). If cytopenia is confirmed, the next step is to establish whether this is due to a reduction in output of cells from the bone marrow (myelosuppression), or to a shortened survival of the affected cell type(s) in the peripheral blood. Important causes of shortened peripheral blood cell survival include bleeding and haemolysis (for red cells), immune neutropenia (for white cells), immune thrombocytopenia or platelet consumption in coagulopathies such as disseminated intravascular coagulation or thrombotic thrombocytopenic purpura (for platelets), and hypersplenism (for all cell lines.) If myelosuppression is suspected, a drug-induced aetiology must then be differentiated from other marrow pathologies such as haematinic deficiency, primary haematological malignancies (e.g. myelodysplasia, leukaemia, lymphoma, myeloma and related disorders), or marrow infiltration with secondary carcinoma, fibrosis or storage disorder.

The diagnostic pathway involves clinical history and examination, the automated full blood count (FBC), and, where indicated, reticulocyte counting, microscopic blood film examination and bone marrow aspirate and trephine biopsy. Table II lists some aspects of a differential diagnostic process.

The simple, rapid and inexpensive screening test of an automated FBC is readily available to any healthcare professional, and confirms or excludes cytopenia(s) when the possibility is suspected. Patients receiving high-risk drug therapy may be having regular monitoring FBCs. In other patients, whether or not they are receiving drug treatment, the availability of the FBC should facilitate its prompt use if there are suggestive symptoms.

Symptoms of cytopenia may be vague and nonspecific, or may be particularly suggestive of haematological disorder. Anaemia presents with tiredness, fatigue, malaise. It may uncover ischaemic symptoms such as angina or claudication, or exaggerate them if already present. It is further

Table II. Differential diagnosis of drug-induced myelosuppression

Mechanism of cytopenia	Diagnosis	Cytopenia	Other blood tests	Bone marrow findings
Myelosupression	Aplastic anaemia	Pancytopenia	Reticulocytopenia	Marked hypocellularity
	Pure red cell aplasia	Anaemia, normal WBC and platelets	Reticulocytopenia	Cellular, absent erythropoiesis
	Megaloblastic anaemia	Anaemia, sometimes leucopenia, thrombocytopenia	Macrocytosis, reticulocytopenia	Hypercellular, megaloblastic erythropoiesis
	Sideroblastic anaemia	Anaemia	Reticulocytopenia	Cellular, ring sideroblasts prominent
Myelosupression or peripheral cell destruction	Agranulocytosis	Severe neutropenia, rapid onset	Normal Hb, platelets	Variable granulocyte representation, absent neutrophils
	Autoimmune neutropenia	Neutropenia, slower onset	Normal Hb, platelets	Left shifted granulocyte maturation
Peripheral cell destruction	Autoimmune haemolytic anaemia	Anaemia	Reticulocytosis, hyperbilirubinemia, positive direct antiglobulin (Coombs') test	Hypercellular, erythroid hyperplasia
	Immune thrombocytopenia	Thrombocytopenia	Normal Hb, WBC	Cellular, abundant megakaryocytes

Hb = haemoglobin level; **WBC** = white blood cell count;

suggested by pallor on examination. Leucopenia is not in itself necessarily symptomatic, but oral ulceration is a typical initial presentation. It may be suggested by unusually frequent or severe infection, or by atypical or opportunistic infection (e.g. oral candidiasis in the absence of previous antibiotic or corticosteroid therapy.) Thrombocytopenia may manifest as easy or spontaneous bruising and/or a purpuric rash.

If anaemia is present, an automated (or manual) reticulocyte count gives an indication of the output from the marrow of newly formed (<48 hours old) red cells into the peripheral blood. A count of $<50 \times 10^9$/L in the face of significant anaemia (haemoglobin level <100 g/L) is suggestive of myelosuppression. An appropriately high reticulocyte count indicates a healthy marrow response and suggests causes of shortened red cell survival such as bleeding or haemolysis. There is no direct counterpart screening test of marrow output for nucleated cells or platelets. The FBC provides additional numerical data concerning the size and haemoglobin content of the red cells. Patterns of abnormality may be typically suggestive of, e.g. haematinic deficiency, haemoglobinopathy or the 'anaemia of chronic disease' associated with inflammation of any cause. There is no specific pattern suggestive of drug-induced myelosuppression but macrocytosis is typical of megaloblastic erythropoiesis.

Blood film examination by an experienced microscopist is mandatory if significant cytopenias are present, and will inform a decision as to whether or not marrow examination is indicated. Marrow examination will confirm the cellularity of the bone marrow and reveal any evidence of megaloblastic or sideroblastic change in addition to excluding any of the other primary or secondary marrow pathologies mentioned above. Cytogenetic analysis of the marrow may rarely reveal clonal abnormalities indicative of myelodysplasia in the absence of definite morphological features. There are no specific tests to confirm a drug-induced aetiology; however, this has to be inferred from the patient's drug history weighted by probability depending on the agents included, and the exclusion of other pathologies.

5.1 Indications for Bone Marrow Examination

A bone marrow aspirate and trephine biopsy under local anaesthetic in an adult is a relatively straightforward procedure for an experienced practitioner. Compared with the FBC it is relatively invasive for the patient. In children, a short general anaesthetic is usually given. The decision to undertake marrow examination should be made in consultation with a haematologist, taking into account the clinical history, examination findings, and the peripheral blood counts and film examination features. Severe or prolonged cytopenias will always merit marrow examination. On the other hand, if a transient moderate leucopenia in a patient receiving, for example, carbimazole for hyperthyroidism exhibits no clinical or peripheral blood features suggestive of any other haematological pathology and resolves promptly and spontaneously on withdrawal of the drug it may not be necessary. As a general principle it is good practice to undertake marrow examination if specific supportive therapy becomes necessary. As well as excluding other pathology, the cellularity and degree of maturation in the marrow can give an indication as to the likelihood and time-scale of recovery. If granulocyte precursors are absent from the marrow, neutrophil recovery is unlikely within 14 days. If there is hyperplasia of early granulocytic precursors but with an absence of mature forms, recovery within 2–7 days following drug withdrawal may be anticipated.[57]

6. Management of Drug-Induced Myelosuppression

Once peripheral blood cytopenias have been confirmed and diagnostic investigations are under way, the drug history will reveal any potential causative agents, and enable discontinuation of any potentially causative drug therapy. Whilst the principles of management and supportive care in marrow failure are logical and straightforward, severe cytopenias are potentially life threatening and management should be undertaken by staff with appropriate expertise and facilities.

6.1 Identification and Withdrawal of Causative Agent

This may be readily apparent in the case of cytotoxic chemotherapy. Idiosyncratic reactions may be suspected by exposure to a drug having an established association with myelosuppression. Newly licensed preparations in the drug history of patients presenting with otherwise unexplained marrow failure should be regarded with suspicion. Any drug with idiosyncratic myelosuppressive effects, which become apparent during phase I, II and III trials is unlikely to achieve a licence, and rare reactions such as idiosyncratic myelosuppression usually only become apparent at postmarketing surveillance.

It is critically important that all potentially implicated drugs are discontinued at the first sign of idiopathic myelosuppression. Unlike with some allergic reactions, cross-reactivity between different drugs of the same class for these reactions is not problematic. It is safer to stop or switch all potentially implicated medication if there is any doubt that it may be involved.

7. Supportive Care

7.1 Expertise and Facilities

Early involvement of healthcare professionals familiar with the treatment of myelosuppressed patients is vitally important in order to minimise the potentially serious risks of this complication. The risk of serious infection is clearly related to the severity and duration of neutropenia. Whilst protocol-based management of initial pyrexial illness in neutropenic patients is well evidence based and increasingly generally available[70] the supportive management of patients with prolonged cytopenias, and specific therapy with immunosuppression or stem-cell rescue are the prerogative of specialised units with appropriate facilities.[71]

7.2 Management of Neutropenia/Infection

7.2.1 Empirical Antimicrobial Therapy

The incidence of severe or opportunistic infection is increased when the neutrophil count is $<1.0 \times 10^9$/L, and significantly greater still at $<0.5 \times 10^9$/L.[72] When neutropenic patients develop fever (single oral temperature >38.3°C; temperature ≥38.0°C for 1 hour) or other signs compatible with infection they should receive empirical therapy with broad-spectrum intravenous antibiotic therapy without delay, as soon as blood specimens and routine surveillance swab and urine culture specimens have been taken.[73] The clinical history and examination findings together with routine chest radiology may indicate the site of infection and guide the choice of initial antibiotic therapy, as will any history of antibiotic allergy. Many different initial regimes are effective and policies are guided by local prevalence and resistance rates. Essential requirements of an appropriate regime in this situation are powerful broad-spectrum activity against Gram-negative organisms including *Pseudomonas aeruginosa*, and sufficient anti-Gram-positive activity to provide safety until culture results are available. Examples include 2-drug regimens with an aminoglycoside and either an antipseudomonal carboxy- or ureidopenicillin or third-generation cephalosporin, or monotherapy with a carbapenem or quinolone. Gram-positive organisms are increasingly frequent causes of bacteraemia in neutropenic patients receiving chemotherapy, partly because of the greatly increased use of indwelling vascular access catheters and an increased severity of mucositis with more intensive regimens.[73] If there are clinical risk factors such as venous catheter-related infection, severe mucositis, documented colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) or previous use of quinolone prophylaxis, then intravenous vancomycin (or teicoplanin[74]) should be incorporated in the initial antibiotic regimen.[70] Otherwise it may be added as part of second-line antibiotic therapy if the fever fails to respond after an initial 48–72 hour assessment period, or if culture results indicate the need. If fever does not respond to first- or second-line antibiotic therapy, empirical broad-spectrum intravenous antifungal therapy with amphotericin B should be considered.[75] Culture, serological testing and computed tomography/magnetic resonance imaging may provide evidence suggestive of fungal infection. Other infections requiring specific therapy, which may account for failure of first-line therapy include *Pneumocytis carinii* pneumonia (PCP), *Clostridium* species colitis, atypical pneumonia and viral infections including herpes viruses and cytomegalovirus.

7.2.2 Prophylactic Antimicrobial Therapy

A number of studies in the 1990s demonstrated that it was possible to reduce the incidence of febrile episodes in neutropenic patients by the administration of prophylactic broad-spectrum oral antibiotics such as cotrimoxazole (trimethoprim-sulfamethoxazole) or quinolones. This did not affect mortality rates, however, and considerations of developing antibiotic resistance mean that antibacterial prophylaxis is not routinely recommended. Cotrimoxazole is indicated for the prophylaxis of PCP[76] in patients with additional risk factors for impairment of T-cell function such as cytotoxic therapy with fludarabine, cladribine or pentostatin. Fungal infection is increasingly common in neutropenic patients and oral candidiasis is a frequent early infection especially if there is cytotoxic-related mucositis, or recent corticosteroid or antibiotic therapy. Oral fluconazole or itraconazole are effective therapy in oral candidiasis, but routine prophylactic use is not recommended except in bone marrow/stem cell transplant patients[77] unless there are high local infection rates or additional individual risk factors.[70]

7.2.3 Use of Colony-Stimulating Factors

Cytotoxic Induced Myelosuppression

The colony-stimulating factors G-CSF and GM-CSF can reduce the severity and duration of neutropenia after cytotoxic therapy.[78-80] Randomised studies have demonstrated a reduced incidence of febrile neutropenia (FN) when the incidence of FN was >40% in the control groups.[81,82] Primary prophylaxis (the automatic prescription of CSF following chemotherapy) can only be justifiably recom-

mended for cytotoxic regimes with an anticipated incidence of FN of >40%, which are very few.[82] Targeted primary prophylaxis for patients with individual risk factors such as other bone marrow disease, previous extensive chemotherapy or radiotherapy, other relevant comorbidity or advanced age may be appropriate.[82,83] Secondary prophylaxis (the administration of CSF following chemotherapy in patients who have had FN with previous courses of the same treatment, or who have had neutropenia of sufficient severity or duration to necessitate dose or schedule modification for potentially curative chemotherapy) directs therapy to those more likely to benefit from CSF support.[76] G-CSF is associated with a lower incidence of adverse effects than GM-CSF in this situation, especially in children.[84] The macrophage stimulating function of GM-CSF may have advantages in the context of fungal infection.

Idiosyncratic Myelosuppression

There are numerous case reports and small series of patients with drug-induced agranulocytosis being treated with G-CSF.[85-88] No prospective randomised studies are available, and it would be virtually impossible to undertake one for this rare and heterogenous condition. Historical control comparisons have been made. Treatment with G-CSF of five patients with clozapine-induced agranulocytosis produced a median time to resolution of 8.2 days compared with 15.7 days for a historical control group.[89] G-CSF is well tolerated and simple to administer. A review of 70 reported cases of drug-induced agranulocytosis treated with G-CSF and GM-CSF indicated a mean time to neutrophil recovery of 5.4 days compared with 10 days from historical data.[90] Experience in the context of cytotoxic therapy is extensive and G-CSF is safe and well tolerated in normal subjects (it is used to mobilise peripheral blood stem cells in healthy donors).[91] The bone marrow appearances may help to identify those who are likely to recover quickly without requiring growth factor support.[57] It would seem reasonable however to prescribe it for idiosyncratic drug-induced agranulocytosis which does not show evidence of neutrophil recovery after 48 hours of drug withdrawal, or where the complication of FN has already occurred.

7.2.4 Management of Anaemia

Anaemia due to myelosuppression is readily correctable by the transfusion of allogeneic red cell concentrates in order to maintain the haemoglobin concentration at an asymptomatic level.[92] Patients with specific additional impairment of T-cell function should receive irradiated blood products to protect them from the risk of transfusion-associated graft versus host disease.[93] Leucocyte depletion of blood products for transfusion reduces the risk of HLA sensitisation, important in patients who may be candidates for regular transfusion or bone marrow transplantation.[94] Epoetin has been shown to reduce transfusion support requirements in patients receiving cytotoxic therapy. The effect was most beneficial for patients with non-haematological malignancies receiving platinum-containing chemotherapy regimens, and its use has been recommended as a safe and effective alternative to transfusion in this situation.[95]

7.2.5 Management of Thrombocytopenia/ Haemorrhage

Prophylactic platelet concentrate transfusion should be considered if the platelet count is $<10 \times 10^9$/L due to myelosuppression.[96] In patients with immune thrombocytopenia due to peripheral destruction (identified by cellular marrow appearances with plentiful megakaryocytes), platelet transfusion is not indicated unless there is life-threatening bleeding. The risk of haemorrhagic complications is greater if the patient is pyrexial, if they have impaired platelet function due to other drug therapy or uraemia, or if invasive procedures are undertaken. A higher count threshold before transfusion is indicated in these circumstances. In a patient who is actively bleeding, transfusion to maintain the count $>50 \times 10^9$/L is justified. Irradiated products may be required as for red cells (see section 7.2.4). HLA-matched platelets may be required for patients who have been sensitised by previous blood product transfusion.

7.2.6 Specific Therapy for Aplastic Anaemia

Specific therapy for prolonged drug induced marrow failure which does not improve after causative drug withdrawal involves consideration of immunosuppressive therapy or bone marrow transplantation, as for idiopathic aplastic anaemia.[97] Such approaches would not normally be considered unless severe cytopenia(s) with marrow hypoplasia were persistent for at least 3 weeks of supportive therapy alone, in order to allow time for potential spontaneous recovery. These therapies are the remit of specialist haematology units. Successful immunosuppressive approaches have included high-dose corticosteroid, antilymphocyte globulin and cyclosporin,[98] this combination with G-CSF,[99] and high-dose cyclophosphamide.[100] Allogeneic marrow or peripheral blood stem-cell transplantation from a histocompatible sibling donor can be very successful with survival rates as high as 90% in one single centre series.[101] General experience suggests a figure of 77%.[102,103] With only a one in four chance of histocompatibility for each sibling, some 70% of patients do not have this option.[104] Matched unrelated donor transplants have poorer outcomes, particularly in adults.[105]

8. Strategies for Prevention/ Early Detection

8.1 Cytotoxic Therapy

Regular peripheral blood count monitoring is standard practice with cytotoxic drugs. The other mainstay of early detection is the education of patients, carers and healthcare staff in the signs and symptoms suggestive of cytopenias, and the importance of prompt blood count confirmation and appropriate management as above. Dose reduction in, or delay before subsequent scheduled courses may be instituted if unexpectedly severe or prolonged cytopenias occur. Primary or secondary prophylaxis with G-CSF for neutropenia and epoetin for anaemia may be appropriate.

8.2 Idiosyncratic Reactions

Early warning rather than prevention is the main goal here. For a small number of drugs with a significant risk of myelosuppression, regular monitoring, as for cytotoxic therapy, is required or desirable (table III). Patient and carer education in the significance of symptoms suggestive of infection, bleeding and anaemia are again important. Monitoring may prevent a minor cytopenia developing into a more severe aplasia by indicating discontinuation of gold or penicillamine therapy where a prodromal gradual count reduction may precede a severe reaction. Monitoring itself will clearly not prevent a suddenly precipitate agranulocytosis with, e.g. antithyroid drugs, which may occur in between even quite frequent monitoring visits. However, it does reinforce patient education in the potential complication, and their access to FBC, increasing the likelihood of early detection.

Use of the antipsychotic clozapine was restricted to patients registered with the Clozaril Patient Monitoring Service, which is run by the drug manufacturer Novartis Pharmaceuticals.[61] Generic clozapine is now available in the US and similar monitoring schemes are run by generic manufacturers (e.g. IVAX Clozapine Patient Registry, Zenith Goldline's Clozapine ALERT Program and Mylan's CLOZAPINE Prescription Access System). Regular FBC are performed by central laboratories and re-

Table III. Some non-cytotoxic drugs for which routine blood count monitoring is justifiable

Drug	Incidence of idiopathic myelosuppression (where assessed)
Gold salts	
Penicillamine	
Azathioprine	
Sulfasalazine	1 in 700 patients in first 3 months; thereafter risk is low
Clozapine	7–8/1000 in first year; 7/10 000 thereafter
Carbimazole	3/10 000/year, mainly in first 3 months of treatment
Thiamazole (methimazole)	
Thiouracils	
Azidothymidine	
Interferon-α	

quire to confirm that the total white cell count is $>3.0 \times 10^9$/L and the neutrophil count $>1.5 \times 10^9$/L, and that significant downward trends in figures above these levels are not occurring, before enough drug supply is issued just to last until the next count is due. Early discontinuation and prompt recognition enabling immediate supportive care and treatment have greatly reduced both the incidence and mortality of severe neutropenia with this useful agent to acceptable levels.[62,106]

Sulfasalazine produces most of its idiosyncratic myelosuppression within the first 3 months of treatment, presumably as susceptible individuals are revealed, and a case can be made for reducing the frequency of surveillance after that time,[107] except perhaps in those at risk of folic acid deficiency.[108]

The case for routine surveillance monitoring with antithyroid drugs is controversial.[109,110] A prospective study in Japan found a 0.4% incidence of agranulocytosis occurring within the first 3 months of treatment with thiamazole or propylthiouracil, and 43 of 55 of the affected patients were detected by routine monitoring before the onset of symptoms.[111] Counts recovered in all the patients, and 29 did not develop any infection. Monitoring clearly allowed prevention of a potentially dangerous complication for a significant group of patients in this study, but the pharmacoeconomic justification for routine monitoring in this situation is not universally accepted.[110]

In addition to FBC monitoring, pretreatment assessment of TPMT either by enzyme activity or genetic markers prior to azathioprine or mercaptopurine treatment, and MTHFR status prior to methotrexate therapy, as discussed in section 2.7, may assist prevention.

Notification of suspected occurrences of drug-induced myelosuppression to national regulatory authorities is an important contribution to prevention, and particularly important for idiosyncratic reactions to new agents.

9. Conclusion

Myelosuppression is a common and anticipated adverse effect with cytotoxic chemotherapy. With other drugs the reaction is rare, but some higher risk agents merit additional vigilance with routine FBC monitoring. Whether or not monitoring is required, patients receiving any drug therapy who develop symptoms suggestive of cytopenias should have a FBC without delay. If cytopenias are confirmed, appropriate further investigation to clarify the cause should be undertaken, and supportive care by staff with the appropriate expertise and facilities should be instituted.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The author has no conflicts of interest that are directly relevant to the contents of this manuscript.

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