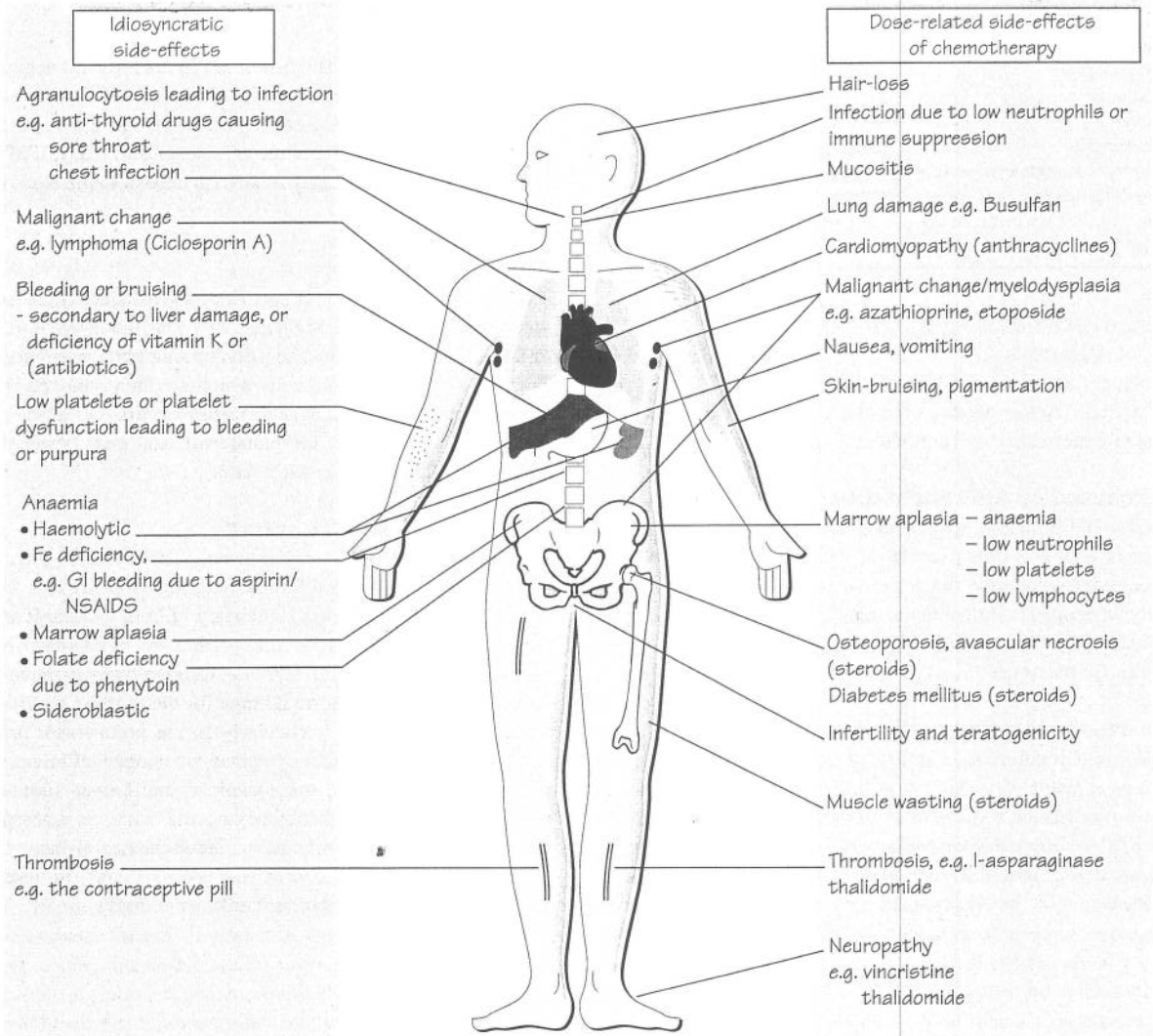
46 Haematological effects of drugs

(a) Drugs may have a wide variety of idiosyncratic side-effects on the haemopoietic system (left-hand panel). Side-effects of chemotherapy are also given on the right-hand panel and are related to the dose/duration of therapy.



Drugs may cause a wide variety of haematological changes (Fig. 46a). Two broad categories of effect occur:

1 Idiosyncratic—i.e. effects which only occur in certain individuals and are independent of the dose.

2 Dose-dependent and predictable effects.

Genetic mechanisms may underlie individual susceptibility to side-effects. Genetic traits may also influence drug metabolism—e.g. some individuals metabolize purines such that certain drugs (azathioprine) are more likely to cause bone marrow suppression.

Recognizing, monitoring and reporting haematologic toxicity is an important part of the marketing and postmarketing surveillance and assessment of new drugs. Mechanisms of haematologic toxicity include:

- direct toxicity of the drug or its metabolites to haemopoietic stem cells or more mature cells;
- induction of immune-mediated damage to haematologic stem cells;
- effects on intermediary metabolism of haematinics or vitamins;
- indirect effects via damage to other organs, e.g. the liver;
- predisposition to malignant change.

Stem cell damage

Pancytopenia occurs in a *predictable* dose-dependent fashion following chemotherapy or radiotherapy. Chemotherapeutic agents which particularly induce marrow hypocellularity include anthracyclines, epipodophyllotoxins, alkylating agents and antimetabolities. Pancytopenia typically occurs 5–8 days after commencement of treatment, its degree is dose dependent, and recovery occurs 10–20 days after commencement of therapy. Growth factors (eg. G-CSF, see p. 9) may be used to accelerate recovery of blood counts.

Idiosynchratic aplastic anaemia occurs rarely (e.g. 1 in 20 000–100 000 individuals exposed to the same drug) and is independent of the dose. Drugs with this potential side effect include antibiotics (e.g. chloramphenicol, sulfonamides), antirheumatic drugs (e.g. gold, indometacin (indomethacin)) and chlorpromazine. It is typically severe, up to 50% of patients do not recover their blood counts, and may require treatment for bone marrow failure (see p. 44).

Anaemia

The commonest form of drug-induced anaemia is iron deficiency due to blood loss. Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids can all cause bleeding from the upper GI tract. Iron absorption is impaired by tetracyclines. Megaloblastic anaemia due to folate deficiency may complicate treatment with anti-epilepsy (e.g. phenytoin) and other drugs. Some drugs, e.g. isoniazid, antagonize vitamin B_6 and cause sideroblastic anaemia and peripheral neuropathy by acting as competitive antagonists; vitamin B_6 must therefore be given with isoniazid.

Drug-induced haemolytic anaemias

These may be immune or non-immune. Immune mechanisms include the following:

- antibody directed against the drug (e.g. penicillin)–red cell membrane complex, the drug acting as a hapten;
- antibody against a drug (e.g. quinidine) with subsequent deposition of the immune complex on red cells;
- stimulation of autoantibody (warm type) production against the red cell, e.g. methyldopa, fludarabine.

Non-immune mechanisms include:

- haemolysis in G6PD deficient individuals (many drugs, see p. 37);
- haemolysis in normal individuals, e.g. dapsone.

White cells

Agranulocytosis may occur as part of aplastic anaemia or in isolation. Idiosynchratic agranulocytosis is seen with antithyroid drugs (e.g. carbimazole), deferiprone (up to 1% of all recipients), antipsychotic drugs (e.g. clozaril), antibiotics (sulfonamide, tetracycline) and anti-inflammatory drugs (e.g. some NSAIDs). Eosinophilia may be seen as part of an allergic reaction to virtually any drug.

Platelets

Drugs can cause an increased risk of bruising and bleeding by interfering with platelet function (e.g. aspirin and NSAID, which inhibit prostaglandin synthesis). Thrombocytopenia may occur as an immune phenomenon (e.g. due to sulfonamides, thiazide diuretics, quinine) or due to direct toxicity, alone or as part of aplastic anaemia (e.g. thiazides, sulfonamides).

Coagulation factors

Alterations may lead to increased risk of bleeding (e.g. aspirin-induced hypofibrinogenaemia) or prolonged antibiotic therapy causing impaired vitamin K absorption. Alternatively, an increased risk of thrombosis may occur, e.g. the contraceptive pill, or hormone replacement therapy may cause an increase in coagulation factors and a reduction in circulating levels of coagulation inhibitors (e.g. protein S).

Drug-induced malignant change

Myelodysplasia may occur following prolonged use of alkylating agents or combination chemotherapy for acute leukaemia or lymphoma. MDS or non-Hodgkin lymphoma may occur following immunosuppressive therapy (e.g. ciclosporin A or azathioprine). Immunosuppressive therapy can cause Epstein–Barr virus-associated lymphoproliferative disorders, particularly after transplantation. Lymphoma has also been reported following phenytoin therapy.