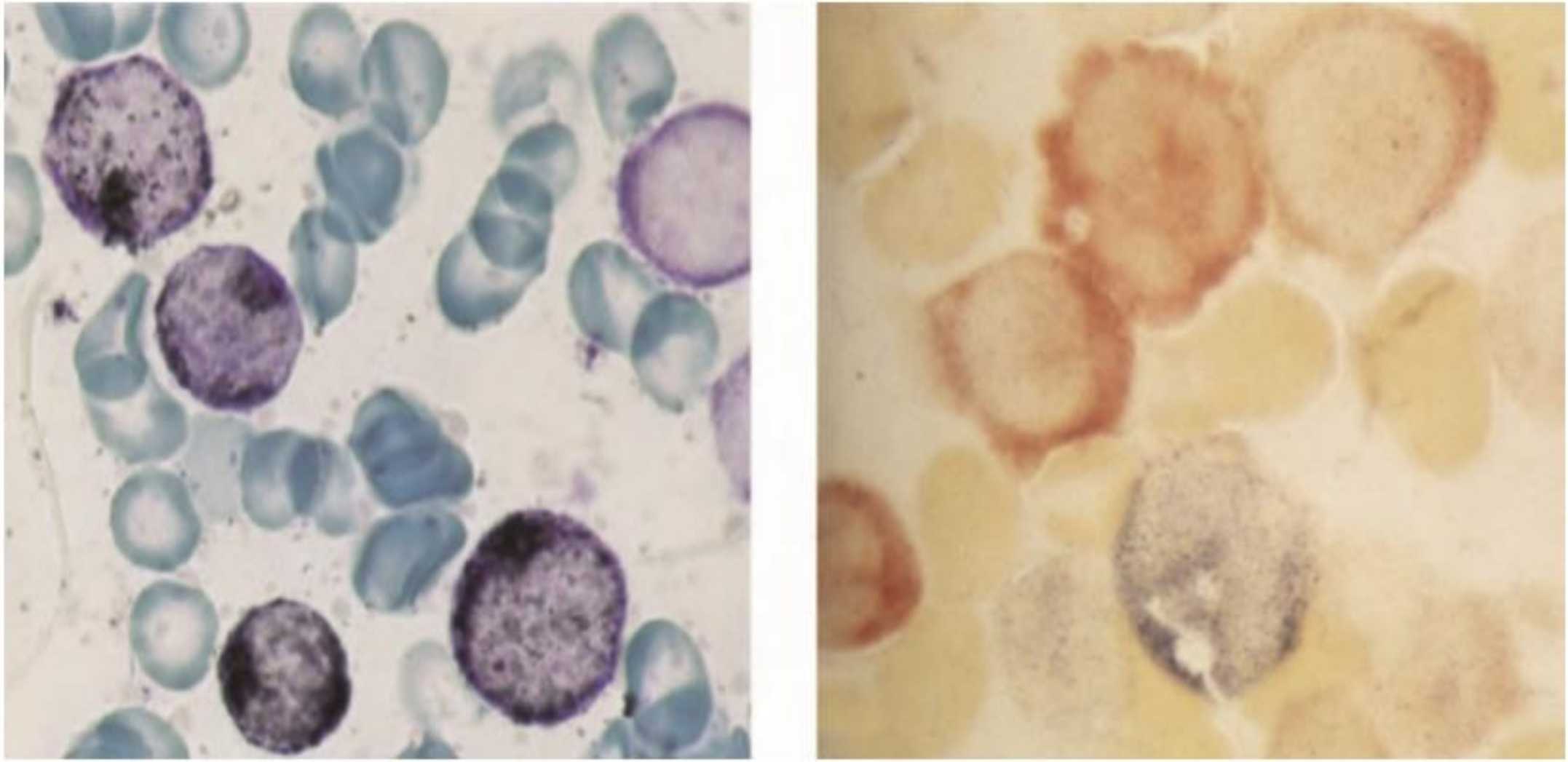
Diagnosis (AML)

- FBC—usually shows leucocytosis, anaemia, and thrombocytopenia. Can show pancytopenia
- Blood film—usually contains blasts.
- BM aspirate—≥20% blasts.
- Trephine biopsy—to exclude fibrosis and multilineage dysplasia.
- Immunophenotyping to diff erentiate AML from ALL: CD3, CD7, CD13, CD14, CD33, CD34, CD64, CD117, cytoplasmic myeloperoxidase (MPO).
- Cytochemistry—MPO or Sudan Black (SB), combined esterase.
- Cytogenetic analysis—to identify prognostic group.
- Molecular analysis—RT-PCR and FISH in selected cases



(a) (b)

Figure 13.6 Cytochemical staining in acute myeloid leukaemia. **(a)** Sudan black B shows black staining in the cytoplasm. **(b)** Myelomonocytic: non-specific esterase/chloracetate staining shows orange-staining monoblast cytoplasm and blue-staining (myeloblast) cytoplasm.

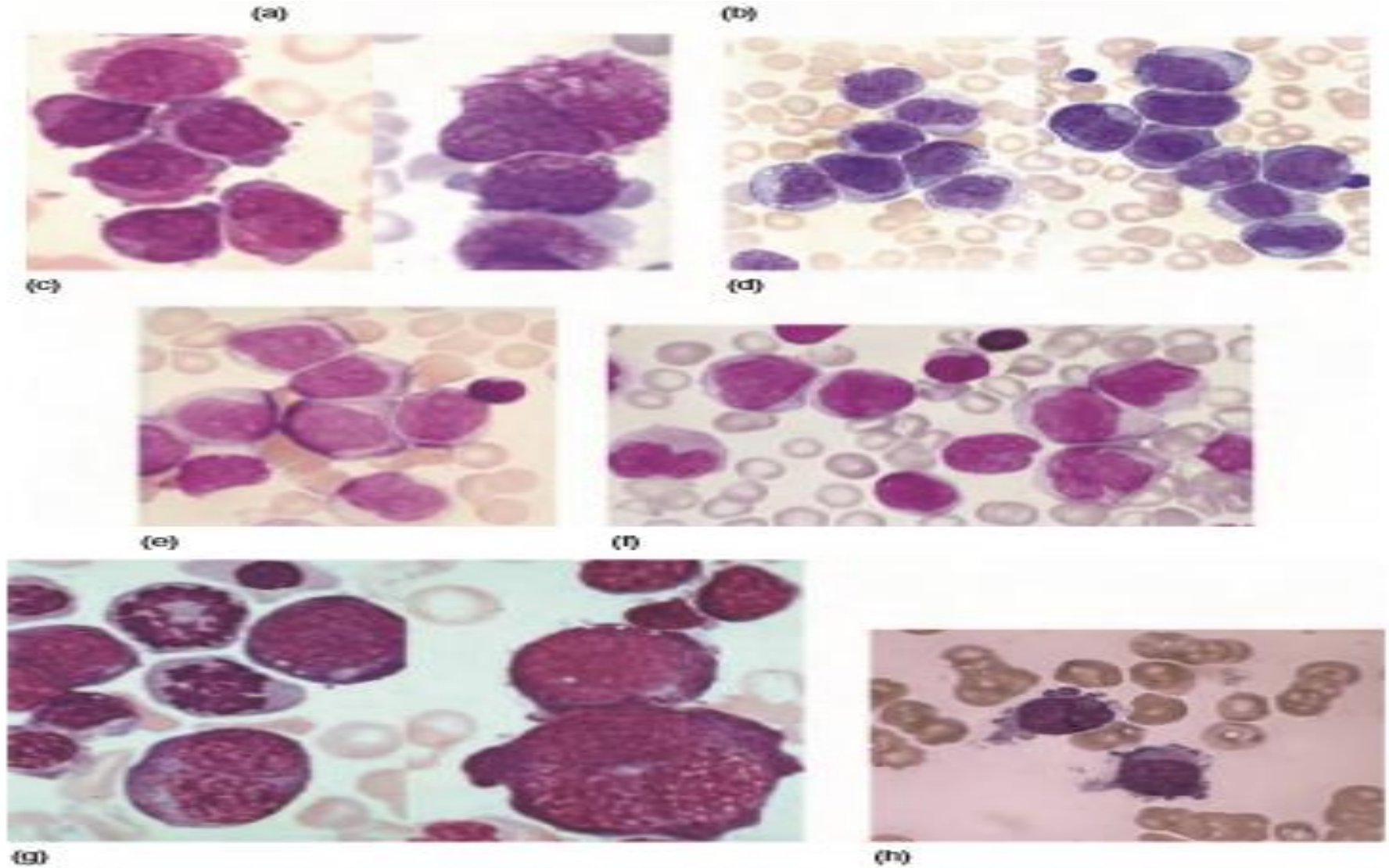


Figure 13.5 Morphological examples of acute myeloid leukaemia. (a) Blast cells without differentiation show few granules but may show Auer rods, as in this case; (b) cells in differentiation show multiple cytoplasmic granules or (c) M_3 blast cells contain prominent granules or multiple Auer rods; (d) myelomonocytic blasts have some monocytoid differentiation; (e) monoblastic leukaemia in which >80% of blasts are monoblasts; (f) monocytic with <80% of blasts monoblasts; (g) erythroid showing preponderance of erythroblasts; (h) megakaryoblastic showing cytoplasmic blebs on blasts.

Cytochemistry

- Formerly the mainstay of leukaemia diagnosis—SB, MPO, and esterase (chloroacetate and non-specifi c esterase (NSE)) stains are +ve in AML and −ve in ALL (<3% blasts +ve). Note: M0 and M7 AML are MPO −ve. NSE is +ve in monocytic cells. Cytochemistry is not essential if 4-colour flow cytometry and estimation of cytoplasmic MPO is available

Six main groups of AML are recognized.

1. AML with recurrent genetic abnormalities encompasses subtypes with specific chromosomal translocations or gene mutations. The detection of these abnormalities defines the tumour as AML and so the diagnostic criteria for this subgroup are relaxed in that the bone marrow blast cell count does not need to exceed 20% in order to make a diagnosis. In general these disorders have a good prognosis.

2. AML with myelodysplasia-related changes. In this group the AML is associated with microscopic features of dysplasia in at least 50% of cells in at least two lineages. The clinical outcome of these patients is impaired in relation to the first subgroup.

3. Therapy-related myeloid neoplasms(t-AML) arise in patients who have been previously treated with drugs such as etoposide or alkylating agents. They commonly exhibit mutations in the MLL gene and the clinical response is usually poor.

4. AML, not otherwise specified. This group is defined by the absence of cytogenetic abnormalities and comprises around 30% of all cases. Mutations in the NPM1 and FLT3 genes are more frequent in those with normal cytogenetics

Immunological markers (flow cytometry) CD13, CD33, CD117 CD11c,14,64 Glycophorin (CD235a) Platelet antigens (e.g. CD41, CD42, CD61) Myeloperoxidase + + (monocytic) + (erythroid) + (megakaryoblastic) + (undifferentiated)

Cytochemistry Myeloperoxidase Sudan black Non-specific esterase

+ (including Auer rods) + (including Auer rods) + in M4, M5

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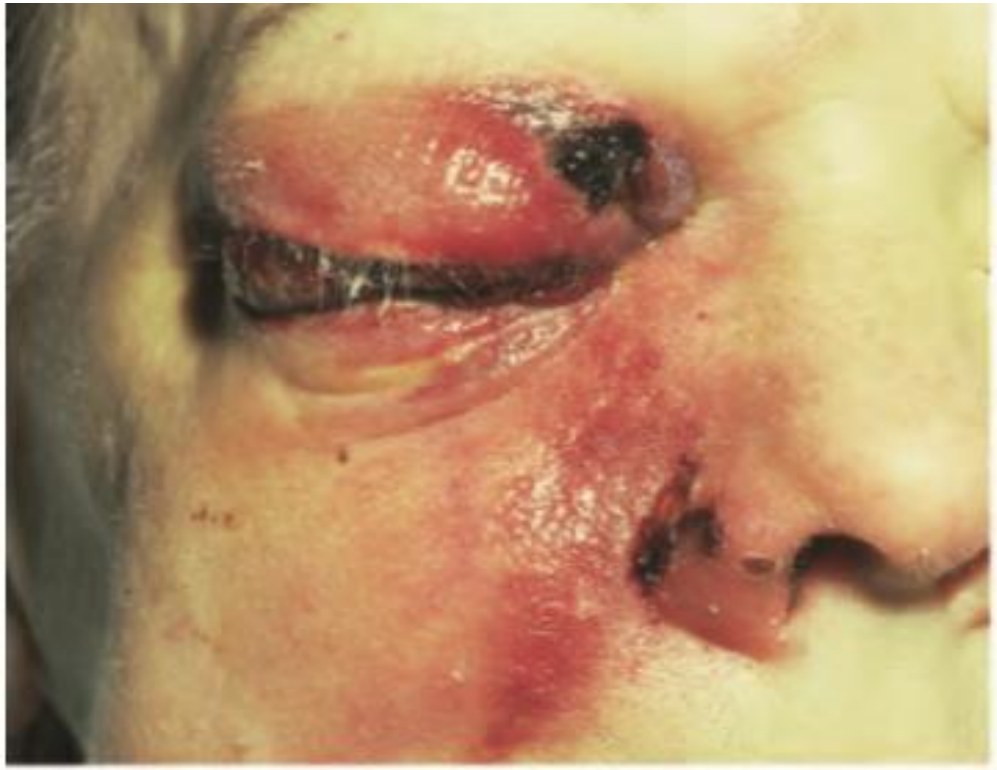
5. Myeloid sarcoma is rare but refers to a disease that resembles a solid tumour but is composed of myeloid blast cells.

6. Myeloid proliferations related to Down's syndrome. Children with Down's syndrome have a



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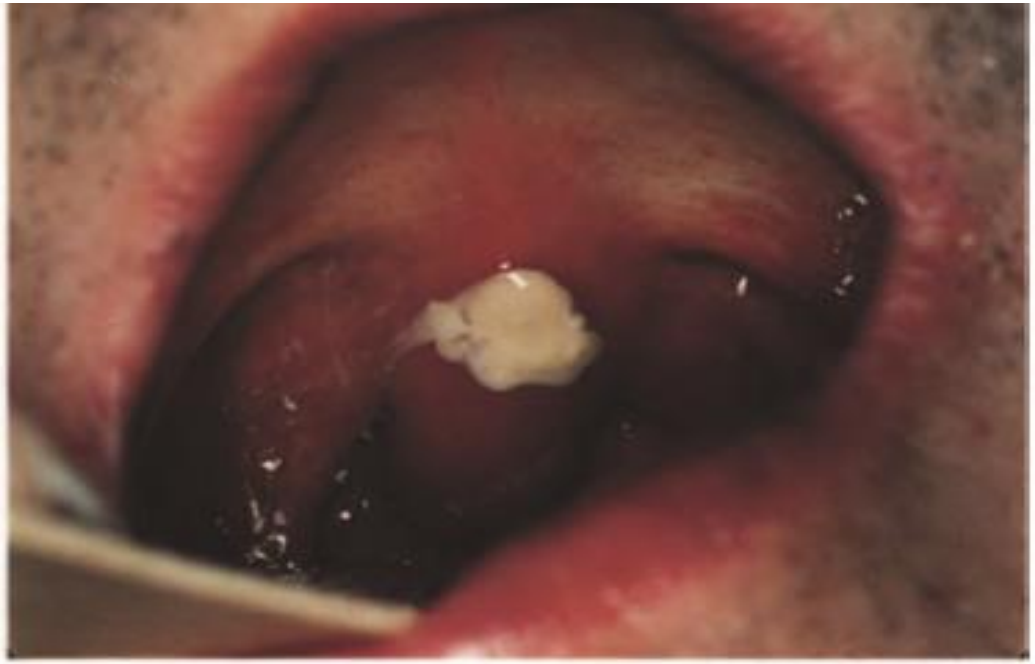
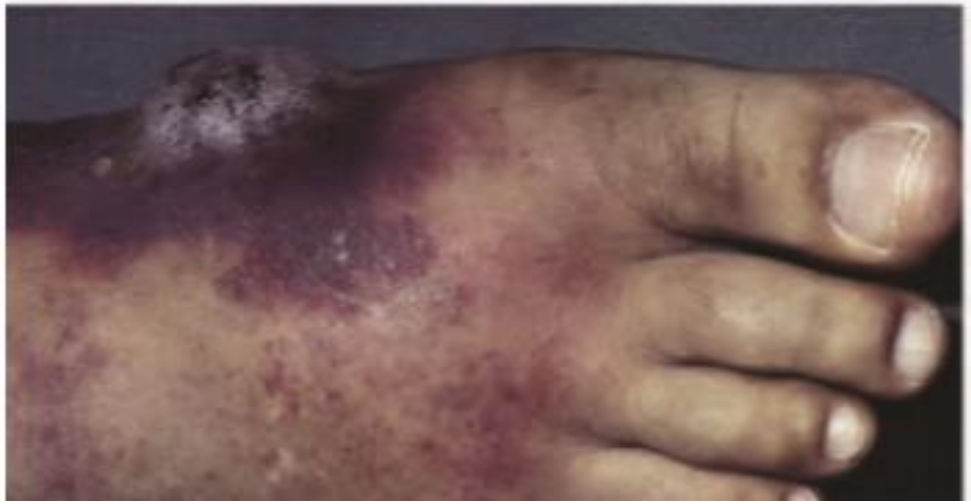
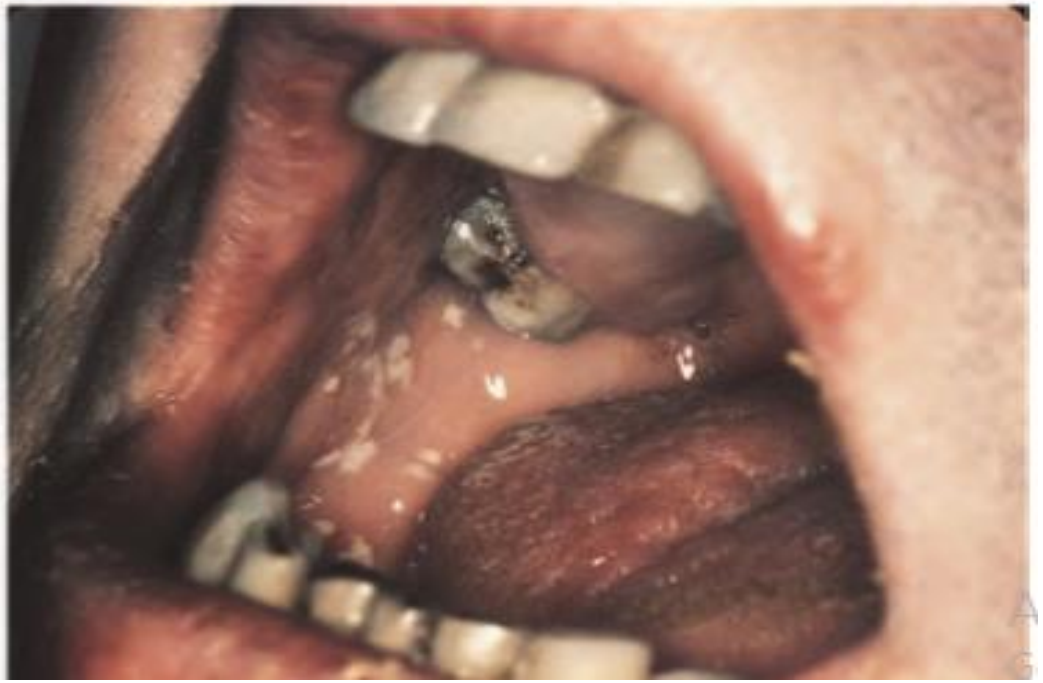
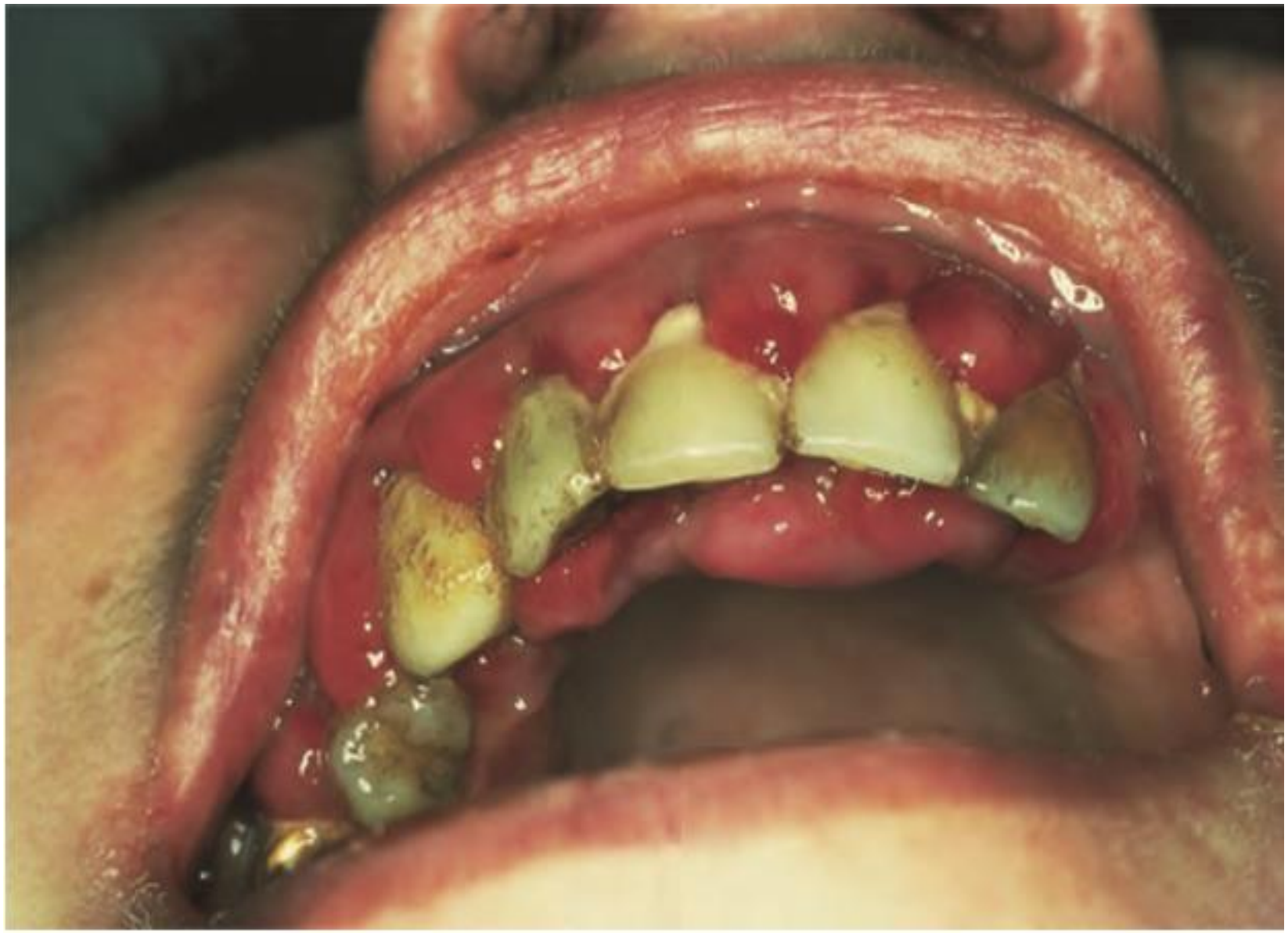








Treatment

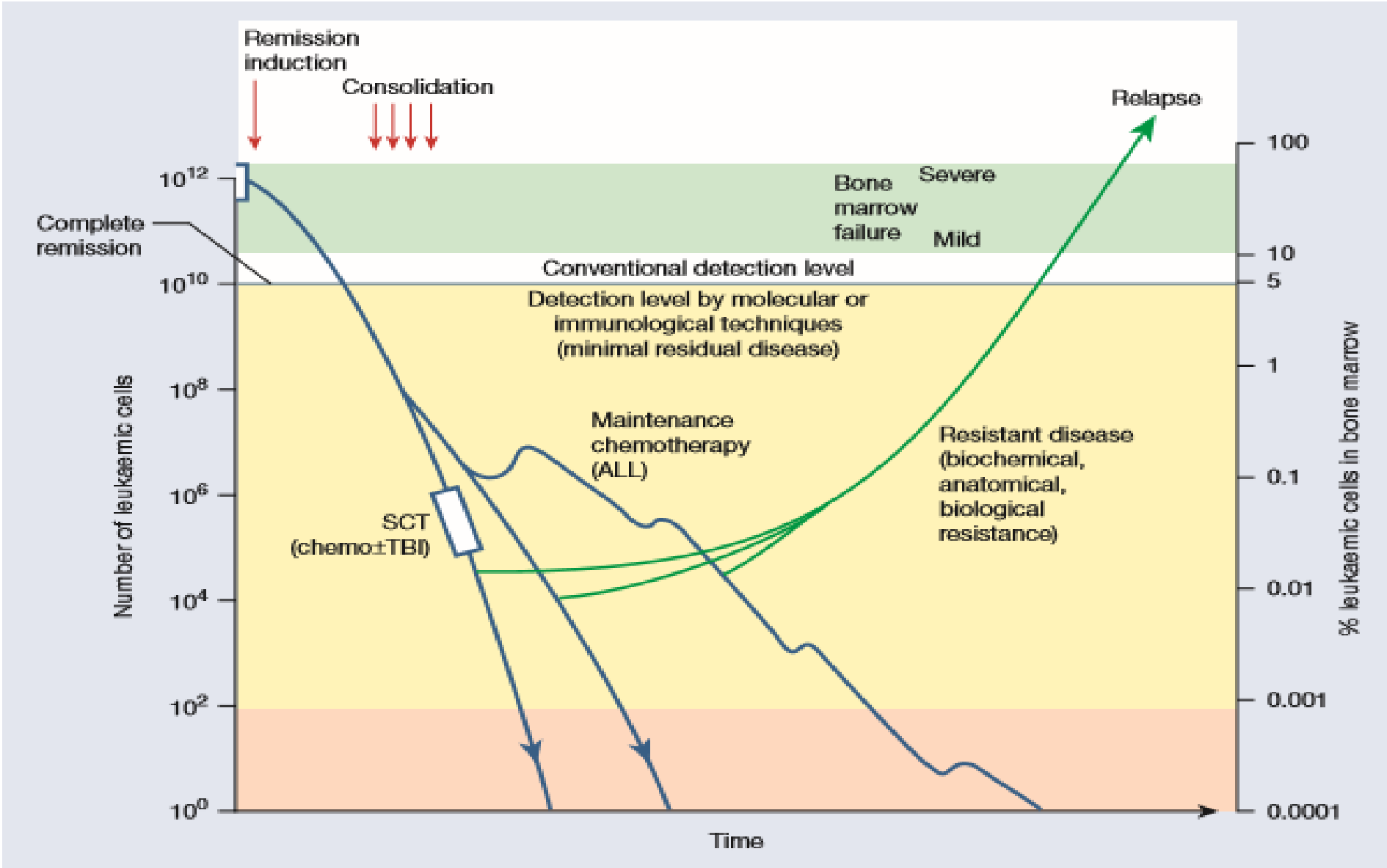
Management is both supportive and specific.

1. General supportive therapy for bone marrow failure and includes the insertion of a central venous cannula, blood product support and prevention of tumour lysis syndrome. The platelet count is generally maintained above 10 × 109/L and the haemoglobin above 80 g/L. Any episode of fever must be treated promptly. Acute promyelocytic leukaemia needs special support.

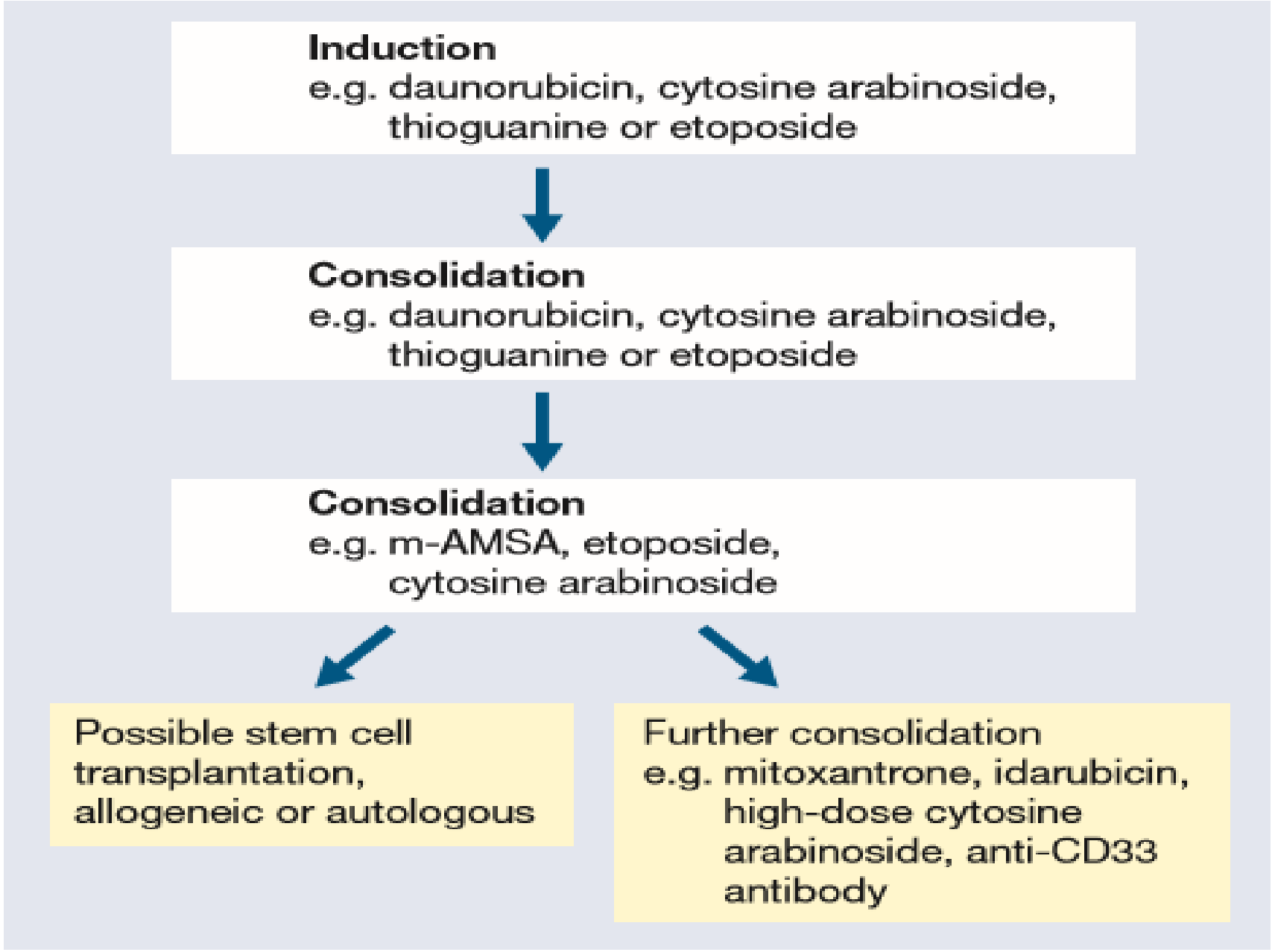
2. The aim of treatment in acute leukaemia is to induce complete remission (less than 5% blasts in the bone marrow, normal blood counts and clinical status) and then to consolidate this with intensive therapy, hopefully eliminating the disease. Allogeneic stem cell transplantation is considered in poor prognosis cases or for patients who have relapsed.

3. Specific therapy of AML is determined by the age and performance status of the patient as well as the genetic lesions within the tumour. In younger patients treatment is primarily with the use of intensive chemotherapy. This is usually given in three or four blocks,

- each of approximately 1 week, and the most commonly used drugs are cytosine arabinoside and daunorubicin (both in conventional or high doses). Idarubicin, mitoxantrone and etoposide are also used in various regimens 13.9). A typical good response in AML. The drugs are myelotoxic with limited selectivity between leukaemic and normal marrow cells, so marrow failure resulting from the chemotherapy is severe and prolonged, and intensive supportive care is required. Maintenance therapy is of no value except in promyelocytic AML with ATRA. CNS prophylaxis is not usually given. New drugs such as FLT3 inhibitors are now being introduced for tumours with FLT3 mutation



ıre 13.8 Acute leukaemia: principles of therapy for AML or ALL (acute lymphoblastic leukaemia); SCT, stem cell transplantation; TBI, body irradiation. The decision for SCT in remission is based on prognostic factors as well as tests for minimal residual disease.



Acute myeloid leukaemia: flow chart illustrating typical treatment regimen.

Patients over 70 years of age.

The median age for presentation of AML is approximately 65 years and treatment outcomes in the elderly are poor because of primary disease resistance and poor tolerability of intensive treatment protocols. Death from haemorrhage, infection or failure of the heart, kidneys or other organs is more frequent than in younger patients. In elderly patients with serious disease of other organs, the decision may be made to use supportive care with or without gentle single-drug chemotherapy, e.g. with low-dose cytarabine, azacytidine or hydroxycarbamide. However, in those otherwise well, combination chemotherapy similar to that used in younger patients may produce long-term remissions and reduced-intensity SCT is increasingly being offered..

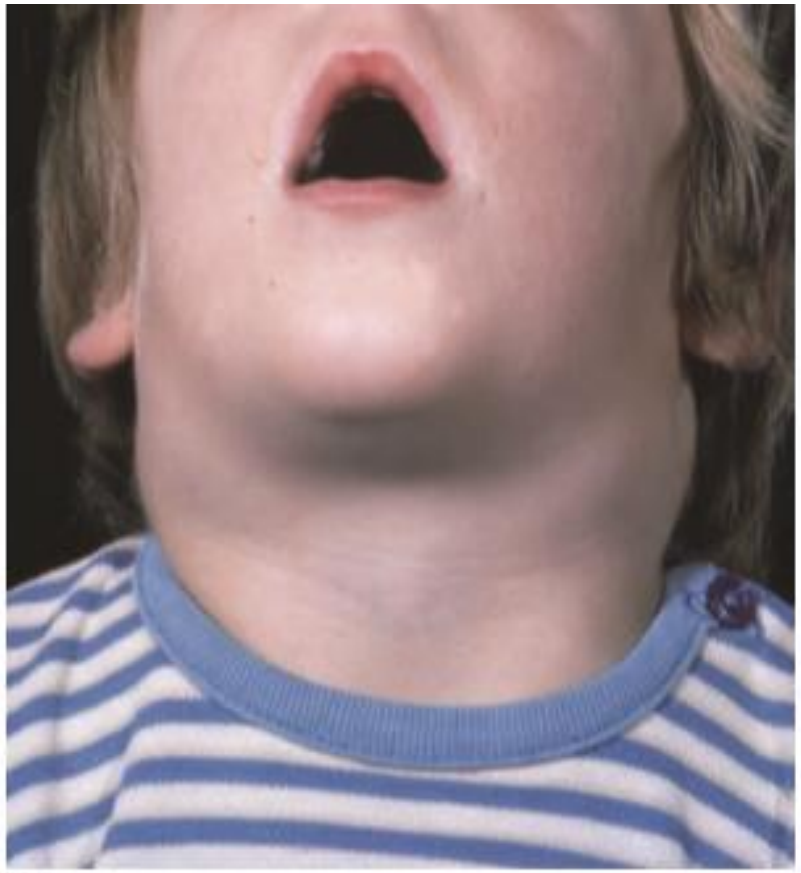
Treatment of relapse:

Most patients suffer relapse and the outlook will then depend on age, the duration of the first remission and the cytogenetic risk group. In addition to further chemotherapy, allogeneic SCT with either standard or reduced-intensity conditioning is usually performed in those patients who can tolerate the procedure and who have a suitable donor. Arsenic trioxide is useful in management of relapse in the promyelocytic variant.

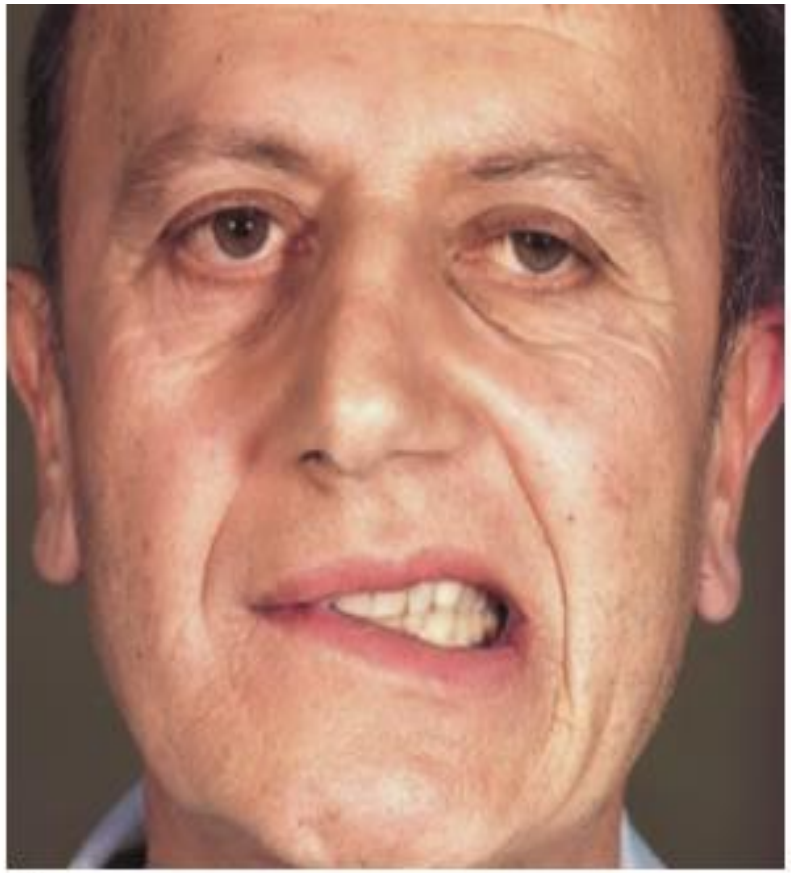
Outcome: The prognosis for patients with AML has been improving steadily, particularly for those under 60 years of age, and approximately one-third of this group can expect to achieve long-term cure. For the elderly the situation is poor and less than 10% of those over 70 years of age achieve long-term remission

Table 17.1 Classification of acute lymphoblastic leukaemia (ALL) according to WHO (modified from WHO 2008; see also Appendix).

B acute lymphoblastic leukaemia with recurrent genetic abnormalities
ALL with t(12;21)
ALL with t(9;22)
ALL with t(11q23; variable)
Hyperdiploidy (>50 chromosomes)
Hypodiploidy (<45 chromosomes)
T- acute lymphoblastic leukaemia
N.B. A minority of patients present with nodal or extranodal masses and <20% blasts in the marrow and are called lymphoblastic lymphoma if the tumour cells resemble those of ALL.



(a)



(b)

Acute lymphoblastic leukaemia. **(a)** Marked cervical lymphadenopathy in a boy. **(b)** Facial asymmetry in a 59-year-old man lower motor neurone seventh nerve palsy resulting from meningeal leukaemic infiltration. Source: Hoffbrand V.A., Pettit J.E

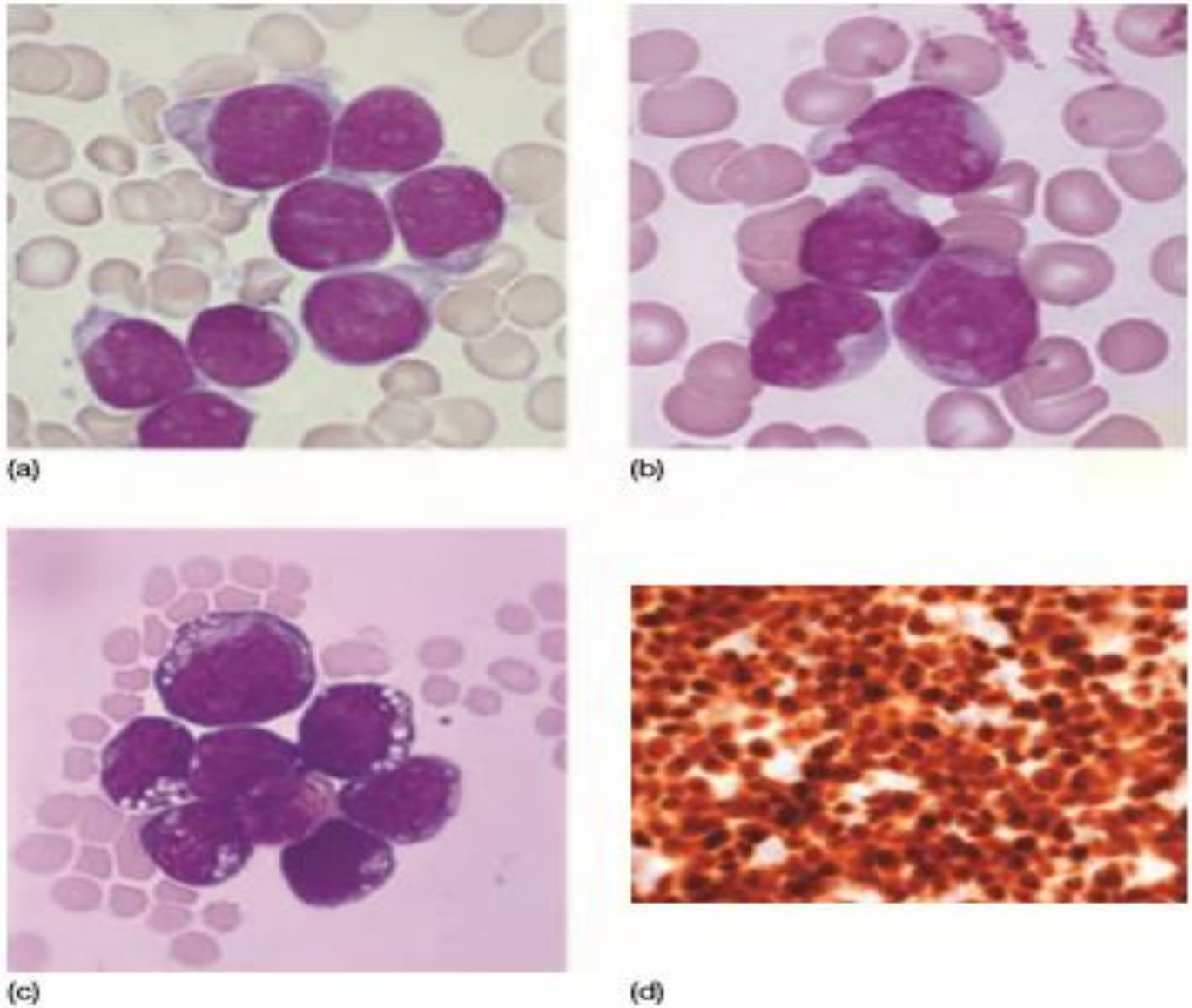


Figure 17.4 Morphology, and immunophenotyping of acute lymphoblastic leukaemia (ALL). **(a)** Lymphoblasts show scanty cytoplasm without granules. **(b)** Lymphoblasts are large and heterogeneous with abundant cytoplasm. **(c)** Lymphoblasts are deeply basophilic with cytoplasmic vacuolation. **(d)** Acute lymphoblastic leukaemia: bone marrow cells staining positive for TdT by immunoperoxidase. Source: Hoffbrand A.V., Pettit J.E. & Vyas P. (2010) Color Atlas of Clinical Hematology, 4th edn. Reproduced with permission of John Wiley & Sons.

Flow chart illustrate the management of ALL