Adult leukaemias
prognostic classification and treatment

Advances in the understanding of leukaemias in adults have led to improved classification on the basis of prognosis and the development of targeted drugs for treatment.

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Leukaemia in adults is not a single disease but a number of different syndromes with widely varying clinical features, prognoses and responses to treatment. In this respect it is unlike childhood leukaemia, which is predominantly acute lymphoblastic leukaemia. All adult leukaemias occur infrequently or rarely, more often in patients over the age of 60 years. However, they require special consideration because of the emotional connotations of the diagnosis, the responsiveness of most forms of leukaemia to therapy, and the need for specialised care.

This article outlines the clinical and diagnostic features of the three major forms of leukaemia affecting adults – acute myeloid leukaemia, chronic lymphocytic leukaemia, and chronic myeloid leukaemia – and discusses recent therapeutic advances in these diseases.

Acute myeloid leukaemia

Presenting features

Most patients with acute myeloid leukaemia (AML) present with clinical features reflecting a rapid onset of failure of normal bone marrow function. Symptoms and signs deriving from one or more of the triad of anaemia, neutropenia and thrombocytopenia will be present in most patients, often dating back only one to three months. Recurrent skin, oropharyngeal or respiratory infections are frequent, as are bruising and purpura

IN SUMMARY

- **Leukaemia in adults is not a single disease but a number of biologically and clinically distinct syndromes.**
- **Advances in the understanding of the molecular basis of leukaemia has improved prognostic classification (most notably in acute myeloid leukaemia) and radically changed therapy (especially in chronic myeloid leukaemia and acute promyelocytic leukaemia).**
- **Accurate diagnosis is critical and hinges on expert haematopathological examination of blood and marrow samples, aided by specialised cytogenetic, flow cytometry and molecular biology studies.**
- **Potentially curative therapy can be offered to younger patients (under 60 years of age) with acute myeloid leukaemia and chronic myeloid leukaemia.**
- **The management of chronic lymphocytic leukaemia depends on whether initial therapy is necessary or not, a decision based on individual clinical factors as well as the biological characteristics of the disease.**
- **General practitioners are well placed for the follow up of chronic lymphocytic leukaemia patients with nonprogressive disease.**

Table 1. Diagnosis of acute myeloid leukaemia in adults

History and physical examination

- Symptoms relating to infection, fever, bone pain, abnormal bleeding tendency, fatigue, splenomegaly, purpura

Blood count

- Haemoglobin – usually reduced
- White cells – variable, may be low, normal range or elevated
- Neutrophils – usually reduced
- Platelets – usually reduced

Blood film

- Usually shows variable numbers of immature leukaemic blast cells

Coagulation tests

- Sometimes evidence of disseminated intravascular coagulation (prolonged PT and APTT, low fibrinogen level, elevated D dimers)

Bone marrow biopsy

- Usually shows increased cellularity, blast cells proportion greater than 20%

Cytogenetic examination of bone marrow cells

- Favourable prognosis group – translocation 8;21, inversion 16, translocation 15;17 (first two associated with core binding factor acute myeloid leukaemia; last one with acute promyelocytic leukaemia)
- Intermediate prognosis group – normal cytogenetics, other simple translocations
- Unfavourable prognosis group – multiple cytogenetic changes, loss of copies of chromosomes 5 and 7

Immunophenotyping studies of bone marrow cells

- Presence of myeloid markers (CDs 13, 33, 65, 117) on leukaemic cells

from low platelet levels. Fatigue is also common, and some patients will experience bone pain and notice weight loss, sweats and fevers.

Most adult AML patients have no recognisable predisposing factors for developing the disease. A few, however, will have a history of exposure to cytotoxic agents (most commonly chemotherapy for other cancers), a prior haematological disorder (such as a myeloproliferative disease) or simply an unexplained abnormal blood count for months or years before the onset of AML.

Diagnosis

Usually the doctor seeing an AML patient initially will be alerted by unusual features in the history, and occasionally by abnormal physical signs such as a petechial rash indicating a low platelet level (Table 1; Figure 1). The blood count is the pivotal investigation: more than one of the three major indices in the blood report – haemoglobin level, white cell count and platelet count – being abnormal is a serious cause for concern. The white cell count may be low, reflecting neutropenia, or may be grossly raised because of the presence of circulating leukaemia cells. In the latter case, the diagnosis will usually be obvious to an experienced morphologist. When pancytopenia is present, a marrow biopsy will establish the diagnosis (Figure 2). In any case, a marrow biopsy will need to be performed for confirmatory immunophenotyping and chromosome analysis.

Classification

Studies correlating chromosomal analysis of leukaemia cells with patient outcome after therapy have shown that the most important factor influencing prognosis is the type of chromosomal abnormalities present at diagnosis.[1] Three main groups of adult AML can be recognised on this basis: a prognostically favourable group, a prognostically unfavourable group and a large proportion with an intermediate outlook.

The favourable group consists mainly of younger patients (under 60 years) and comprises two main forms of AML: acute promyelocytic leukaemia (in which the chromosomal abnormality is a translocation between chromosomes 15 and 17) and so-called core binding factor AML (translocation between chromosomes 8 and 21, or inversion in chromosome 16). Together these make up around one-third of adult AML cases, and they are important because of the younger age of onset and good response to therapy.

The unfavourable group comprises less than 20% of cases of AML overall, and is seen more frequently in older patients. The remaining adult AML patients make up the group with an intermediate prognosis.

Management

People with newly diagnosed AML need urgent referral to a specialty haematology unit, of which there are 30 or so around Australia. Aside from the cytogenetic risk category (prognosis classification), the main consideration in the management of AML is age. Patients older than 65 years generally have AML that is more resistant to cytotoxic drugs, are more likely to have other medical conditions that compromise leukaemia therapy, and are generally less able to tolerate intensive treatment for their leukaemia, compared with younger patients. Some elderly patients will be offered palliative treatment for these reasons.

The majority of AML patients should be treated with intensive combination chemotherapy regimens with the intention to cure. This usually involves lengthy inpatient stays for supportive care with blood products and antibiotics. Chemotherapy for AML currently involves the pyrimidine analogue cytarabine (Cytarabine [DBL], Cytarabine Injection), an anthracycline antibiotic such as idarubicin (Zavedos), and often the podophyllotoxin etoposide (Etopophos, Etoposide

Injection, Etoposide Injection [DBL], Vepesid). Brief intensive courses of these drugs are given to induce remission. Multicentre clinical trials in this country have shown that remission of AML is achieved within a month in about 80% of patients under 60 years of age, that about 10% of patients die of treatment-related complications and that a similar number have drug-resistant disease.[2]

Achievement of remission rapidly restores normal bone marrow function and hence normalises the blood count. Further chemotherapy is then given to consolidate the remission; high doses of cytarabine have been shown to produce the best results. A few patients will have a suitably matched related donor and will be suitable for an allogeneic stem cell transplant in first remission. The remainder require regular follow up and blood counts. Some 40% of younger patients (under 60 years of age) will remain in remission indefinitely. The remainder will develop a relapse of their leukaemia, usually within 12 to 18 months, and unless bone marrow transplantation is an option, further treatment then becomes palliative.

Acute promyelocytic leukaemia

A clinically distinct subcategory of AML, acute promyelocytic leukaemia accounts for about 15% of AML cases (almost always in patients under the age of 60 years), and deserves special consideration. Many patients present with serious bleeding problems due to severe thrombocytopenia and disseminated intravascular coagulation.

The translocation between chromosomes 15 and 17 that is the molecular basis of this disease alters the function of a receptor protein for vitamin A derivatives (retinoids) in the cell nucleus. This change in retinoid receptors has been exploited therapeutically with the use of synthetic retinoids (particularly *all trans* retinoic acid – also known as tretinoin [Vesanoid]), which have been shown in clinical trials to rapidly control acute promyelocytic leukaemia. Oral administration of *all trans* retinoic acid induces maturation in the leukaemia cells and remission in most cases.[3] Addition of idarubicin further improves the outcome; unpublished data from Australian clinical trials on retinoid therapy show survival rates of over 70%, which is a dramatic improvement from before the introduction of this therapy about 15 years ago, when 70% of patients died of this disease.

Chronic lymphocytic leukaemia

Presenting features

Chronic lymphocytic leukaemia (CLL) occurs with increasing frequency in patients over the age of 50 years, and is probably the most common of the adult leukaemias, with an incidence of around four new cases per 100,000 population each year. The presenting features are diverse. With the more widespread use of blood tests, a substantial number of new cases are diagnosed by chance after the discovery of an unexplained lymphocytosis. More commonly, patients present with lymphadenopathy, recurrent infections, unexplained fever or evidence of bone marrow failure.

Diagnosis

Diagnosis is based on the full blood count and morphological examination of the blood smear, and confirmed by flow cytometry immunophenotyping studies

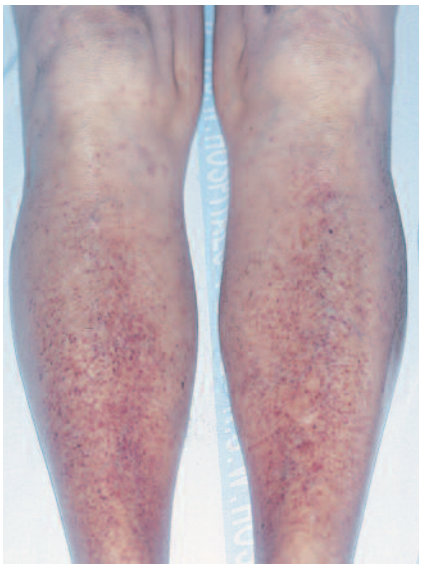

Figure 1. Petechial rash indicating a low platelet count in a patient with acute myeloid leukaemia.

(Table 2). The blood count shows an absolute lymphocytosis, and the blood smear reveals that these are relatively mature cells, although they are fragile when spread on a glass slide, resulting in 'smudge' cells (Figure 3). In early stages of the disease, the haemoglobin and platelet count are normal; in advanced cases, anaemia and thrombocytopenia are frequent. The lymphocyte count is highly variable, from barely above the normal range in some patients to grossly elevated in patients with advanced disease.

Immunophenotyping reveals the

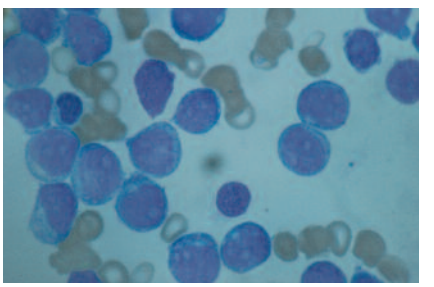

Figure 2. May–Grünwald–Giemsa-stained bone marrow smear showing immature leukaemic blast cells, confirming the diagnosis of acute myeloid leukaemia.

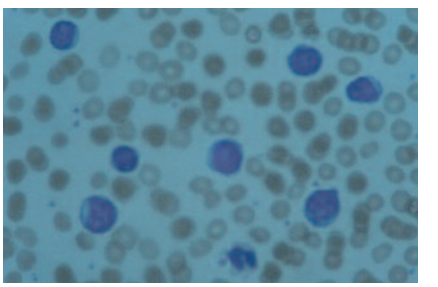

Figure 3. May–Grünwald Giemsa-stained blood smear showing increased mature lymphocytes in chronic lymphocytic leukaemia.

Table 2. Diagnosis of chronic lymphocytic leukaemia

History and examination
- Fatigue, recurrent infection, fevers and sweats, lymphadenopathy, splenomegaly

Blood count
- White cells – normal range or elevated
- Lymphocytes – above normal range (lymphocytosis)
- Haemoglobin – usually normal range for age, sometimes reduced
- Platelets – may be normal or reduced

Blood film
- Shows increased mature lymphocytes and 'smudge cell'

Direct antiglobulin test
- Positive in around 10% of cases

Serum protein electrophoresis
- May show a paraprotein at low concentration, or reduced normal immunoglobulin levels

Immunophenotyping studies of blood lymphocytes
- Characteristic pattern is CD19+, CD5+, CD23+, weak CD20+, weak monoclonal surface Ig+

Bone marrow biopsy
- Not usually necessary, but will show lymphocytosis >40% and nodular or diffuse increase in lymphocytes in trephine sections

Lymph node biopsy
- Not usually necessary, but if done will generally show features of diffuse small lymphocytic lymphoma.
- Occasional transformation to high grade lymphoma

underlying biology of the disease. CLL is a B-cell tumour, like most of the non-Hodgkin's lymphomas, but has a very characteristic phenotype. The cells express the major B-cell markers CD19 and, less strongly, CD20, but also express the marker CD5, which is usually found on T-cells. Immunoglobulin is also weakly expressed on the surface of CLL cells, and is restricted to one light chain form, either kappa or lambda. Finally, the activation marker CD23 is also present. This CD5+, CD19+, CD23+, κ+, or λ+ phenotype is the 'signature' of CLL, and readily distinguishes it from other lymphoproliferative diseases. Bone marrow biopsy in a newly diagnosed CLL patient does not add any further diagnostic or prognostic information over that obtained from blood tests, and most haematologists now resist the temptation to carry out such biopsies.

Staging

Staging is of relevance in CLL in that it provides some guidance about the likelihood of therapy being required. Unlike AML, where the disease process is relentlessly progressive and all patients require treatment, many patients with CLL will have nonprogressive disease for extensive periods of time, and some will never require treatment at all over decades of observation.

Two staging systems, the Rai and Binet classifications, offer the clinician assistance in making therapeutic and prognostic decisions for the newly diagnosed CLL patient. Both systems are pragmatically based on a mix of clinical factors (lymphadenopathy and splenomegaly) and laboratory factors (anaemia and thrombocytopenia). Patients lacking these features are likely to have non-progressive disease initially and a life expectancy of greater than 10 years, and probably will not require treatment at diagnosis.

Management

The appropriate course of action for a newly diagnosed patient with CLL lacking features of advanced stages of disease is to watch and wait. The patient needs to be carefully counselled that, although CLL is a neoplasm, the disease usually runs a benign course and that clinical trials in the past have shown that intervening early with therapy can, in fact, be detrimental in asymptomatic patients. Management should consist of regular follow up, with documentation of infections, enlargement of spleen and lymph nodes and progress blood counts. Triggers for considering initiation of treatment include a doubling of the lymphocyte count in less than 12 months, a significant fall in haemoglobin or platelet levels, rapid or symptomatic lymph node or splenic enlargement, unexplained fevers and a striking increase in infectious episodes (Table 3). Repeat flow cytometry studies or bone marrow biopsies have no place in the follow up of CLL cases. Much of the follow up is most appropriately performed by the general practitioner, following initial advice by a specialist, with referral back to that specialist if certain predefined events occur.

In contrast, patients with evidence of marrow failure at diagnosis will have progressive disease, a life expectancy of two to three years, and a need for immediate treatment.

Recent scientific advances should further improve the determination of the prognosis in individual CLL patients at diagnosis, and hence assist the making of decisions about when to treat these people. The absence of mutations in the variable region of the immunoglobulin gene in the CLL cells, and the presence of two markers, CD38 and ZAP-70, detectable by flow cytometry, has been shown to correlate with poor survival and progressive disease. These biological markers may soon be incorporated into the decision-making process for CLL.[4]

Treatment

CLL has not been considered a curable disease. Some patients never require specific treatment and enjoy long survival, but treatment is eventually necessary for most patients because of progression, usually for the indications discussed above. The mainstay of therapy for the past

Table 3. Triggers for therapeutic intervention in chronic lymphocytic leukaemia

- Lymphocyte count doubles in less than 12 months
- Onset of progressive anaemia or thrombocytopenia
- Development of progressive symptomatic lymphadenopathy or splenomegaly
- Constitutional symptoms – unexplained fevers and sweats, weight loss, recurrent infections

50 years has been the oral alkylating agent, chlorambucil (Leukeran). Repeated brief courses of this drug control the disease process with minimal side effects in most cases. Corticosteroids such as prednisone (Panafcort, Sone) probably contribute little. Newer agents, in particular the purine analogues fludarabine (Fludara) and cladribine (Leustatin), produce more rapid responses in untreated patients but do not prolong survival and are expensive; their role outside clinical trials is for patients whose disease progresses after initial chlorambucil therapy. Ultimately, it is usual with heavily pre-treated patients to resort to combination chemotherapy protocols, such as those used for lymphoma; the underlying intent, however, is palliation.

Recent developments perhaps afford a more hopeful situation in the future for the treatment of CLL. Strikingly high complete response rates in previously untreated patients have been reported by clinicians at the University of Texas, using combined therapy with fludarabine, the alkylating agent cyclophosphamide and the chimeric monoclonal antibody rituximab, which binds to the B-cell antigen CD20.[5] These responses and their durability are being examined in multicentre clinical trials, and if confirmed will provoke a major re-assessment of the way that CLL is managed in the future.

Chronic myeloid leukaemia

Presenting features

Chronic myeloid leukaemia (CML) is a rare but fascinating disease. Although it affects only about one in 100,000 people each year, its importance lies in the model it has created in translational scientific research and rational drug design.

CML presents with the characteristics of advanced cancer (fatigue, anorexia, sweats, weight loss, bulky splenomegaly) rather than with the features of bone marrow failure, as in AML. Anaemia is often present, but infections or bleeding are not.

Table 4. Diagnosis of chronic myeloid leukaemia

History and examination
- Symptoms of advanced cancer, i.e. fatigue, anorexia, sweats, weight loss, bulky splenomegaly

Blood count
- White cells – pronounced leucocytosis (mostly mature neutrophils)
- Haemoglobin – usually reduced
- Platelets – often raised

Blood film
- Shows mature neutrophils and some immature cells.
- Eosinophilia and basophilia usually present

Bone marrow biopsy
- Shows similar features to blood film

Cytogenetic examination of bone marrow cells
- Presence of Philadelphia chromosome

Diagnosis

The blood count is very characteristic in CML, with a pronounced leucocytosis in all patients (Table 4). Most leucocytes are mature neutrophils, but there are also many immature cells (at all stages of mat - uration). Eosinophilia and basophilia are also usually present. The platelet count is often raised, and mild to moderate anaemia is common.

The bone marrow biopsy shows similar features to the blood film, reflecting advanced myeloproliferative disease. The most important aspect of the diagnostic work up is examination of bone marrow chromosomes. Virtually all CML cases have the Philadelphia chromosome, an acquired abnormality in bone marrow stem cells. This characteristic chromosomal abnormality, first described 40 years ago, results from the exchange of large pieces of genetic material between chromosomes 9 and 22. The reciprocal translocation involves the moving of most of a crucial regulatory gene, the Abelson oncogene (*c-abl*), from chromosome 9 to the breakpoint cluster region (*bcr*) on chromosome 22. This breakage and reattachment leads to a fused *abl–bcr* gene on a chromosome 22 that is shorter than normal (the Philadelphia chromosome) and a chromosome 9 that is longer than normal. The protein product from the *abl–bcr* gene functions improperly, resulting in uncontrolled proliferation of the abnormal stem cells.

Treatment

The treatment of CML has recently been revolutionised by improved understanding of the molecular basis of the disease enabling targeted therapy, namely the development of a compound to specifically inhibit the function of the abnormal Abelson gene. The recent introduction of this drug, imatinib mesylate (Glivec), into clinical practice has dramatically changed the management of CML. Striking responses, including the elimination of all Philadelphia chromosome-positive cells from the marrow, have been reported in around two-thirds of newly diagnosed cases treated with imatinib mesylate.[6] There is now a real possibility that CML may prove to be a curable condition with relatively simple and safe drug therapy that is targeted at a genetic abnormality found only in the leukaemic cells.

Other forms of leukaemia in adults

Other leukaemias are much rarer in adults than those described above.

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) occurs in adults as well as in children, but only at around 10% of the frequency of AML. ALL in adults is much more resistant to therapy than the childhood form, and treatment results are much poorer than current outcomes with paediatric ALL.

Hairy cell leukaemia

Hairy cell leukaemia is a rare, relatively benign B-cell disease that usually presents with splenomegaly and pancytopenia. It responds well to the purine analogue cladribine.

Conclusion

Major changes have occurred in the diagnosis, classification and treatment of the various forms of leukaemia in adults over the past 10 years, largely based on improved understanding of the molecular basis of these diseases. Further scientific advances are likely to improve the outlook for these patients in the future, based on better prognostic grouping within specific diseases and better targeted therapies. MT

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