



Treatment of adult leukaemias

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Summary

Improved understanding of the molecular causes of leukaemia is altering the approach to management. Acute myeloid leukaemia is managed with chemotherapy according to the patient's prognostic factors, but stem cell transplantation may be an option. Imatinib is now available for the treatment of chronic myeloid leukaemia, but whether it should be preferred over transplantation is uncertain. When chronic lymphocytic leukaemia progresses, it can be managed with chemotherapy, in which fludarabine has an increasing role.

Key words: antineoplastics, imatinib, stem cell transplantation.

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Introduction

Leukaemia in adults is not a single disease entity. It includes a number of different diseases with widely varying molecular and cytogenetic features, clinical characteristics, prognoses and responses to treatment. The most common leukaemias in adults are acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia. (Acute lymphoblastic leukaemia occurs in adults as well as children, but at only around 10% the frequency of acute myeloid leukaemia. Although adults are given the same treatment as children, the outcomes are worse.)

Over the past decade there have been major advances in the diagnosis, classification and management of leukaemia in adults. This is due largely to improved understanding of the molecular basis of these diseases. Improvements in supportive care, the introduction of targeted therapies and increasing use of non-myeloablative conditioning regimens for allogeneic stem cell transplantation have all transformed the treatment of patients with leukaemia. This means that more patients may be offered treatment and that more can be expected to survive for longer periods.

Acute myeloid leukaemia

The incidence of acute myeloid leukaemia increases with age. It accounts for 80% of adult acute leukaemias. Most patients present with clinical features of bone marrow failure such as recurrent infection, bleeding and fatigue. Many experience bone

pain, weight loss, sweats and fevers. While the majority have no predisposing factors to explain the development of the disease, some patients will have a history of a haematological disorder (such as myelodysplasia) or exposure to cytotoxic drugs.

Studies of outcomes after treatment for acute myeloid leukaemia have shown that the most important prognostic factor is the type of cytogenetic abnormality present at diagnosis.¹ There are three main prognostic groups:

- a favourable group (30%) comprising patients with acute promyelocytic leukaemia and patients with acute myeloid leukaemia with chromosomal translocations involving the core-binding factor genes [t(8;21), inv(16)]
- an unfavourable group (20%) comprising patients with complex cytogenetic abnormalities and with abnormalities of chromosomes 5, 7, 11
- an intermediate group (50%).

Other than the cytogenetic risk category, the main determinant of management is the patient's age. Patients older than 65 years are more likely to have drug-resistant disease and frequently have major comorbidities. They are less able to tolerate intensive chemotherapy, so they are often offered palliative therapy, supportive care and/or palliative chemotherapy with drugs such as oral hydroxyurea, oral etoposide or intermittent intravenous cytosine arabinoside.

Younger patients with acute myeloid leukaemia require treatment with intensive chemotherapy, which is generally given in a specialist haematology unit. Chemotherapy for acute myeloid leukaemia currently involves the pyrimidine analogue cytarabine arabinoside. This is given alone in high doses or in lower doses in combination with an anthracycline (such as idarubicin or daunorubicin) and a podophyllotoxin (etoposide). A treatment course consists of induction therapy followed by 1–3 cycles of consolidation therapy. Multicentre studies show that about 80% of patients under 60 years of age achieve remission, 10% die of treatment-related complications and 10% have primary resistance. Overall, 30–45% of patients remain disease-free long term.² There are limited data to support maintenance therapy for acute myeloid leukaemia.

Allogeneic haematopoietic stem cell transplant (see box) may be an option in first complete remission for patients with HLA*-identical sibling donors. Patients with poor risk factors may be offered a transplant during their remission from either

* HLA human leucocyte antigen

sibling or unrelated donors. Transplantation is the treatment of choice for patients with relapsed disease who achieve a second complete remission. If haematopoietic stem cell transplantation is not an option following relapse, the patient is generally given palliative treatment.

Acute promyelocytic leukaemia

Acute promyelocytic leukaemia accounts for about 15% of all cases of acute myeloid leukaemia (almost always in patients under the age of 60). It results from a translocation between chromosomes 15 and 17. This alters the function of a receptor protein for vitamin A derivatives (retinoids) in the cell nucleus and ultimately prevents apoptosis.

The combination of a synthetic retinoid (all-*trans*-retinoic acid (tretinoin)) and the anthracycline idarubicin, induces maturation and apoptosis of leukaemic cells. This leads to remission in most cases and to long-term disease-free survival in over 70% of patients.³ Arsenic trioxide has also shown promise in the treatment of *de novo* and relapsed/refractory disease. Its role in therapy is the subject of intense research interest.

Chronic myeloid leukaemia

Chronic myeloid leukaemia accounts for 7–15% of all adult leukaemias. It is thought to result from the clonal transformation of a haematopoietic stem cell and is historically significant because it was the first disease in which a specific chromosomal abnormality was directly linked to pathogenesis.

In chronic myeloid leukaemia a reciprocal translocation of the Abelson oncogene (c-abl) from chromosome 9 to the breakpoint cluster region (bcr) on chromosome 9 leads to the

formation of a new fusion gene (bcr-abl) on chromosome 22 (the Philadelphia chromosome). This in turn leads to the production of an abnormal protein product (bcr-abl fusion protein) with increased tyrosine kinase activity which functions to promote cell survival and proliferation and to inhibit apoptosis.

Chronic myeloid leukaemia is characterised by leucocytosis, thrombocytosis and splenomegaly, although 40% of patients are asymptomatic. Chronic myeloid leukaemia has three phases: chronic, accelerated and blastic. The natural history is progression from a 'benign' chronic phase to fatal blast crisis over three to five years.

The aim of treatment is to eliminate all evidence of the Philadelphia chromosome or bcr-abl mRNA from the bone marrow and blood (as detected by polymerase chain reaction (PCR) or fluorescence *in situ* hybridisation (FISH)). Long-term survival is most likely in patients who achieve at least a complete cytogenetic response (no Philadelphia chromosome-positive cells detectable in bone marrow).

Initial treatment generally consists of hydroxyurea. This oral cytotoxic drug is effective in reducing the elevated white cell count, but it does not prolong survival. Until recently, most patients were treated with hydroxyurea, busulfan, interferon alfa and/or cytosine arabinoside, with allogeneic haematopoietic stem cell transplant being offered to a younger patient when an HLA-compatible donor is available.

The decision to offer transplantation is generally based upon consideration of the patient's age, phase of the disease and the availability of a suitable donor. Younger patients (under 55) who receive a transplant from an HLA-identical sibling donor during the chronic phase and within a year of diagnosis have a 70% chance of cure. The risks of transplantation are greater in other situations and even in those with the best prognosis the transplant-related mortality is still 5–10%.

Imatinib

The treatment of chronic myeloid leukaemia has recently been revolutionised by the introduction of targeted therapy. Imatinib mesylate is an orally-administered tyrosine kinase inhibitor directed against the bcr-abl fusion protein. It induces complete haematological response and complete cytogenetic response (absence of Philadelphia chromosome) in approximately 75% of newly diagnosed patients.

Despite its early promise, approximately 10% of patients are primarily resistant to imatinib and a further 15–20% may develop resistance after initially responding to the drug.⁴ (Resistance is generally due to point mutations in the bcr-abl kinase region.⁵) Despite these reservations, the advent of molecular therapy means that there is now a distinct possibility that chronic myeloid leukaemia may eventually prove to be a curable condition.

Haematopoietic stem cell transplantation

- Uses multipotent haematopoietic progenitor cells (stem cells) as part of therapy aimed at eliminating underlying disease and restoring normal haematopoietic and immune function
- May be allogeneic (another individual acts as a donor) or autologous (the patient acts as their own source of stem cells)
- Allogeneic transplants may source stem cells from related or unrelated volunteer donors
- Stem cells may be obtained from bone marrow, peripheral blood or umbilical cord blood
- The degree of HLA* identity (match) between the donor and the recipient determines both the choice of donor and the likelihood of adverse outcomes following transplant
- The risks of transplant-related mortality, graft failure, infection and graft vs host disease are lower with transplants from HLA-identical sibling donors.

The question of whether patients should be treated initially with imatinib or transplantation remains unresolved. Many haematologists argue that transplantation remains the only proven cure for chronic myeloid leukaemia and that it should continue to be offered to all younger patients with an HLA-identical sibling donor. Others argue that all patients should have a trial of imatinib and molecular monitoring of their response, with allogeneic haematopoietic stem cell transplantation offered to those who develop disease progression or fail to show a major cytogenetic or a significant molecular response to imatinib.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia is the most common type of leukaemia in the industrialised world, accounting for 40% of all leukaemias in people over 65 years old. Whereas previously many patients presented with lymphadenopathy or symptoms related to bone marrow failure, nowadays over 90% of cases are diagnosed in asymptomatic patients after a blood test is performed for another reason. The median age at presentation is 65–70, but 20–30% of patients are aged below 55 at diagnosis. In most patients the aetiology of chronic lymphocytic leukaemia cannot be established. However, there is an association with some industrial pollutants, and the first-degree relatives of patients with chronic lymphocytic leukaemia are about five times more likely to develop the disorder than the general population.

Chronic lymphocytic leukaemia results from a monoclonal expansion of mature lymphocytes. The malignant clone demonstrates a characteristic phenotype, with cells expressing CD5, CD19, CD20, CD23, light chain restriction and, in cases associated with a poor prognosis, CD38. These findings are sufficiently specific for chronic lymphocytic leukaemia that a bone marrow examination is no longer considered necessary to make a definitive diagnosis.

Chronic lymphocytic leukaemia is generally incurable without allogeneic transplantation. It often progresses slowly, so treatment is generally reserved until there is clear evidence of disease progression, such as progressive bone marrow failure, autoimmune cytopenia, progressive splenomegaly, bulky lymphadenopathy, frequent infections or systemic symptoms. The choice of therapy depends on whether one is aiming for palliation or for complete remission in the hope that this will translate into prolonged survival.

Options for initial therapy include single drug chemotherapy with chlorambucil, cyclophosphamide or the purine analogue, fludarabine. Recent randomised trials have shown that fludarabine leads to higher complete response rates and greater response duration, but not to improved survival when compared with chlorambucil.⁶ These results have led to the increasing use of fludarabine in multidrug regimens.

The most widely used combination includes fludarabine, cyclophosphamide and the anti-CD20 monoclonal antibody, rituximab, given over three days each month for three to six months. Over 90% of patients respond to this regimen, with 70% attaining a complete response, compared to a complete response rate of less than 5% with chlorambucil alone.⁷ Early reports suggest that this may translate into prolonged survival, although this remains to be shown in long-term studies. The major limitation of fludarabine-based regimens is the risk of infection due to the profound immunosuppression associated with such regimens.

There are a number of treatment options available for relapsed or refractory disease including fludarabine, cyclophosphamide and rituximab, cyclophosphamide-vincristine-prednisolone, the same drugs combined with doxorubicin (CHOP), and the monoclonal antibody, alemtuzumab.

Recent studies suggest that allogeneic transplantation with reduced intensity conditioning may offer the best possibility of long-term disease-free survival. However, this is associated with considerable mortality and morbidity and is really only an option for patients aged under 65 years.

Conclusion

Increased understanding of the molecular basis of leukaemia has led to major changes in the way that it is diagnosed, classified and treated. In recent years the development and clinical use of drugs, such as imatinib, and targeted therapies has, in specific patient populations, dramatically improved the chances of disease response and survival. Likewise, advances in transplantation have reduced the early toxicity associated with this procedure and made it an option for more patients. Continuing research into the molecular pathogenesis of leukaemia seems likely to lead to the introduction of new diagnostic techniques and new multidrug therapeutic regimens over the coming years.

References

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

7. Most patients with chronic lymphocytic leukaemia present with the clinical features of bone marrow failure.
8. Chronic myeloid leukaemia is caused by a genetic abnormality.

Book review

Therapeutic Guidelines: Palliative Care. Version 2.

Melbourne: Therapeutic Guidelines Limited; 2005. 369 pages. Price: \$39, students \$30, plus postage

Greg Crawford, Clinical Head of Palliative Care, Lyell McEwin Health Service, Adelaide

The new edition of *Therapeutic Guidelines: Palliative Care* builds on the excellent first edition. This small pocket-sized text is a vital part of the *Therapeutic Guidelines* stable. The published version is very user-friendly and I am looking forward to loading the mini computer version, which is now available, onto my personal organiser.

The *Palliative Care* second version has some changes in format and a tightening of the overall presentation. The order and format of chapters has been streamlined and minor changes only add to the usefulness of this text.

The order of chapters reflects the challenges of caring for people with life-limiting illnesses. There is considerable space given to principles, care of the provider of palliative care, ethical issues and communication. Then follow important guidelines regarding community care and other practical factors. The major symptom groups in order of significance and prevalence are then covered with comprehensive consideration of not only pharmacological therapeutics but all possible interventions.

The chapter on Emergencies has moved further up the contents table and many might wonder what is an emergency in

palliative care. The obvious conditions covered were spinal cord compression, superior vena cava obstruction, acute airways obstruction, haemorrhage and acute confusion. The need to recognise these is paramount and then further management should be decided in the context of the clinical situation, the patient, and their wishes – the total picture. As always, relief of distress remains a paramount issue.

A new chapter on intercurrent illnesses has been written. This is a useful addition and explores the interaction of the life-limiting illness and medical comorbidities. The psychological impact of changing long-term medications was dealt with in a clear and logical progression and reminds us of the need to 'negotiate changes to medication over time rather than making sudden sweeping changes'.

The chapter on pain covers this increasingly complex and fascinating area in a clear, logical and approachable manner.

The new version of *Therapeutic Guidelines: Palliative Care* comes with my high recommendation – not only for relatively inexperienced practitioners but also for those more experienced whose primary focus is not end-of-life care. This small book is also a good summary for those of us whose core practice is with people living with a life-limiting illness. I would recommend this text as a useful resource and an accessible update for all clinicians. Good symptom management and the active involvement of the patient and family in care, particularly at the end of life, are core principles for clinicians of all disciplines and experience.