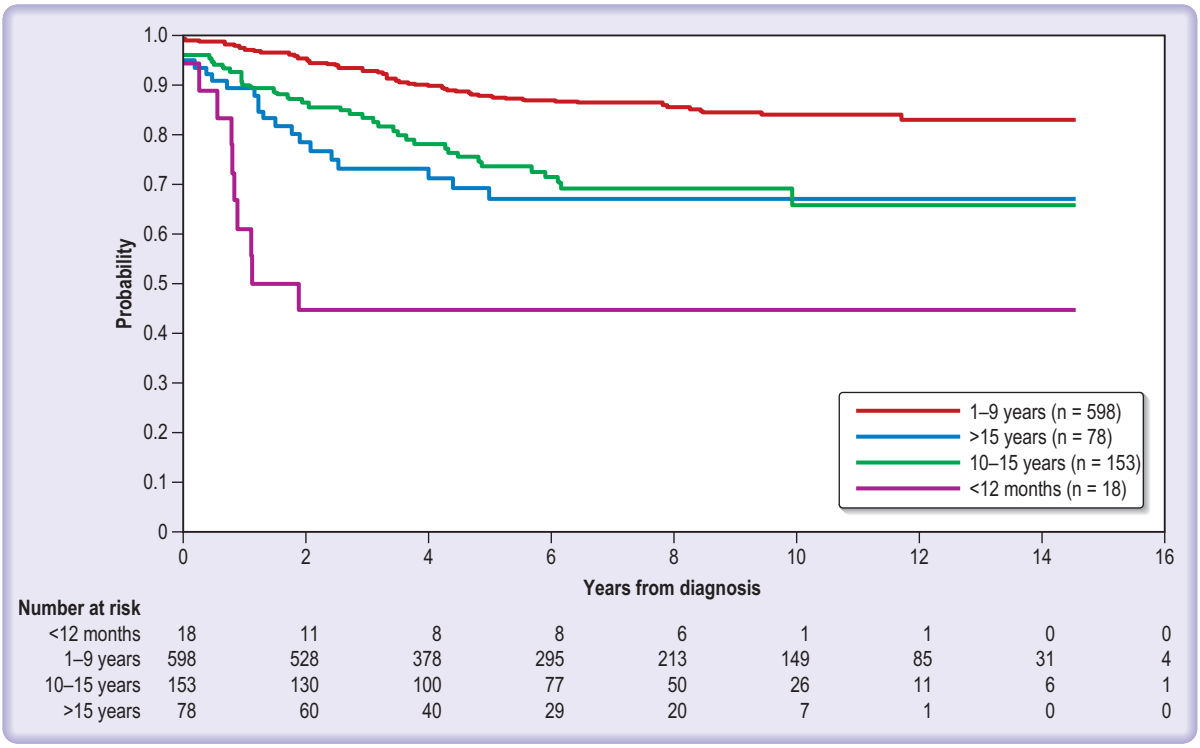

Fig. 9.9 **Overall survival in 2628 children with newly diagnosed ALL** participating in consecutive studies conducted at St Jude Children's Research Hospital from 1962 to 2005. From Pui C-M, Robinson LL, Lock T. Acute lymphoblastic leukaemia. *Lancet* 2008; **371:** 1030–1043, figure 3 with permission from Elsevier.

Prognosis (Fig. 9.9)

The prognosis of ALL in childhood is now excellent: complete remission is achieved in almost all, with up to 80% being alive without recurrence at 5 years. Failure occurs most frequently in those with high blast count and t(9;22) translocation.

The situation is far less satisfactory for adults, the prognosis getting worse with advancing years. Co-morbidity and t(9;22) translocation increases in frequency with age. Overall the complete remission rate is 70–80%, failure being due partly to resistant leukaemia and partly to failure of supportive care. Failure to achieve complete remission with first-line therapy carries a very poor prognosis. If CR can be achieved with new therapies, it should be consolidated with sibling or possibly even unrelated donor transplantation despite the high risk of graft-versus-host disease. Between 30% and 40% of patients continue in durable first remissions, resulting in approximately 25–30% overall patient cure.

As with AML, most recurrences occur within the first 3 years and the outcome is extremely poor. Second remissions, though usually achieved, are rarely durable except following allogeneic transplantation. Isolated extramedullary recurrences, however, may be cured.

CHRONIC LEUKAEMIAS

Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia (CML), which accounts for about 14% of all leukaemias, is almost exclusively a disease of adults with the peak of presentation being between 40 and 60 years and is characterized by the presence of the Philadelphia chromosome (Fig. 9.10). Unlike the acute leukaemias which are either rapidly reversed or rapidly fatal,

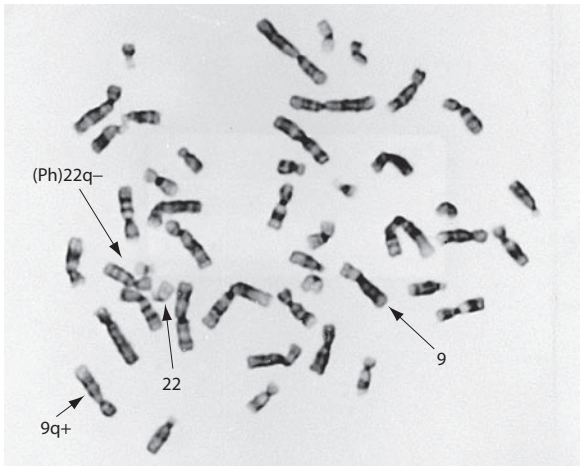

Fig. 9.10 **Philadelphia chromosome.** This is formed by a reciprocal translocation of part of the long arm (q) of chromosome 22 to chromosome 9. It is seen in 90–95% of patients with chronic myeloid leukaemia. The karyotype is expressed as 46XX, (9;22)(q34;q11).

CML has a more slowly progressive course which if not initially cured will be followed eventually by blast crisis (90% myeloid, 20% lymphoid) or myelofibrosis and death after 3–4 years.

Clinical features

CML usually presents in the chronic phase and some patients have no symptoms. Symptoms include:

- symptomatic anaemia (e.g. shortness of breath)
- abdominal discomfort due to splenomegaly

- weight loss
- fever, sweats, in the absence of infection
- headache (occasionally) due to hyperleucocytosis
- bruising, bleeding (uncommon), priapism.

Signs include:

- pallor
- splenomegaly, often massive
- lymphadenopathy (uncommon, when found suggests blast crisis)
- retinal haemorrhage due to leucostasis.

Investigations

- **Blood count**. Hb low (normochromic and normocytic) or normal, WBC raised (usually >100 × 10^9/L), platelets low, normal or raised.
- **Blood film**. Neutrophilia with the whole spectrum of myeloid precursors including occasional blasts. Elevated basophils and eosinophils.
- **Bone marrow aspirate**. Increased cellularity, increased myeloid precursors. Cytogenetics reveals t(9;22) translocation (the Philadelphia chromosome) (Fig. 9.10).
- **Fluorescein-in-situ hybridization (FISH)** or reverse transcriptase polymerase chain reaction (RT-PCR) are used to demonstrate the cytogenetic/molecular abnormality. These are also used to quantitatively monitor response to therapy.
- **Leukocyte alkaline phosphatase** is usually reduced.

Management

Imatinib, a tyrosine kinase inhibitor that specifically blocks the enzymatic action of the BCR-ABL fusion protein, is first-line treatment for the chronic phase. It has replaced alpha-interferon. Imatinib produces a complete haematological response in over 95% of patients, and 70–80% of these have no detectable BCR-ABL transcripts in the blood. Event-free, and overall, survival appear to be better than for other treatments. Imatinib can be continued indefinitely.

In the acute phase (blast transformation) most patients have only a short-lived response to imatinib, and other chemotherapy as for acute leukaemia is used in the hope of achieving a second chronic phase.

Side-effects of imatinib, which usually are well tolerated, include nausea, headaches, rashes and cytopenia. Resistance to imatinib as a single agent may develop as a result of secondary mutations beyond the t(9;22). The use of second generation tyrosine kinase inhibitors, dasatinib and nilotinib, may restore haematological or molecular remissions in those patients in the chronic phase that have primary or acquired resistance to imatinib.

Stem cell transplantation (SCT)

Allogeneic haemopoietic stem cell transplantation can cure approximately 70% of chronic phase CML patients. SCT was choice therapy for young patients with an HLA matched donor, but this has changed in the light of the success of imatinib therapy. It is now only used in those with an inadequate response to imatinib or those that have disease progression on therapy. There are many potential complications with an allogeneic transplantation approach; death may occur as a result of graft-versus-host disease (GVHD) or opportunistic infection, and the decision to proceed is based upon a balance of risk.

Factors making complications more likely include:

- increasing age
- SCT in acute phase
- prolonged interval from diagnosis to transplantation
- degree of histocompatibility between donor and recipient.

Graft-versus-leukaemia effect plays a role in the increased survival following SCT so that reduced-intensity transplantation is being more frequently used.

Chronic lymphocytic leukaemia (CLL)

This is the commonest leukaemia, occurring predominantly in later life and increasing in frequency with advancing years (median age of presentation between 65 and 67 years). It results from the clonal expansion of small lymphocytes and is almost invariably (95%) B cell in origin. The majority of patients are asymptomatic, identified as a chance finding on a blood count performed for another indication. Other patients, however, present with the features of marrow failure or immunosuppression. The median survival is about 10 years, and prognosis correlates with various clinical features at presentation (Table 9.15). These clinical features simply represent differences in the biology of the disease, and a number of cytogenetic and molecular abnormalities are now recognized as being of prognostic significance (see below). A pre-malignant condition, *monoclonal B cell lymphocytosis* (MBL), occurs where there are less than the 5 × 10^9/L B cells required for a diagnosis of CLL. Some of these have CLL phenotype and may progress to CLL.

Clinical features

The majority of patients are asymptomatic at presentation. Common symptoms are:

- recurrent infection because of (functional) leucopenia and immune failure (reduced immunoglobulins)
- anaemia due to haemolysis or marrow infiltration
- painless lymphadenopathy
- left upper quadrant discomfort (from splenomegaly).

The commonest findings on examination are:

- anaemia
- fever (due to infection)
- generalized lymphadenopathy (may involve single area)
- hepatosplenomegaly, sometimes massive.

However, none of these may be present.

Investigations

- **Blood count**. Hb normal or low; WBC raised, and may be very high; with lymphocytosis (criteria for diagnosis > 5 × 10^9/L), platelets normal or low.
- **Blood film**. Small or medium sized lymphocytes. May see smudge cells in vitro.
- **Bone marrow**. Reflects peripheral blood, often very heavily infiltrated with lymphocytes.
- **Immunophenotyping** shows mainly $CD19^+$, $CD5^+$, $CD23^+$ with a weak expression of CD20 and CD79b and surface immunoglobulin (kappa and lambda light chains).
- **Cytogenetics/FISH analysis** are not essential for diagnosis but may help in the assessment of prognosis.

Table 9.15 The Rai and Binet staging systems for chronic lymphocytic leukaemia*

System and stage	Risk	Manifestations	Percent of patients	Median survival (years)	Recommended treatment
Rai staging system					
0	Low	Lymphocytosis	31	>10	Watch and wait
I	Intermediate	Lymphadenopathy	35	9	Treat only with progression†
II	Intermediate	Splenomegaly, lymphadenopathy, or both	26	7	Treat only with progression†
III	High	Anaemia, organomegaly	6	5	Treatment indicated in most cases
IV	High	One or more of the following: anaemia, thrombocytopenia and organomegaly	2	5	Treatment indicated in most cases
Binet staging system					
A	Low	Lymphocytosis, <3 lymphoid areas enlarged‡	63§	>10	Watch and wait
B	Intermediate	≥3 Lymphoid areas enlarged‡	30	7	Treatment indicated in most cases
C	High	Anaemia, thrombocytopenia or both	7	5	Treatment indicated in most cases

*Lymphocytosis is present in all stages of the disease.
†Progression is defined by weight loss, fatigue, fever, massive organomegaly and a rapidly increasing lymphocyte count.
‡Enlarged lymphoid areas may include the cervical, axillary and inguinal lymph nodes; the spleen or liver may be enlarged.
§Stage A includes all patients with Rai stage 0 disease, two-thirds of patients with Rai stage I disease and one-third of those with Rai stage II.
From Dighiero G, Binet JL. When and how to treat chronic lymphocytic leukaemia. *New England Journal of Medicine* 2000; **343**: 1800. Copyright © Massachusetts Medical Society. All rights reserved.

- **Coombs' test**. May be positive if there is haemolysis.
- **Immunoglobulins**. Low or normal.

Prognostic factors

The clinical course of CLL is variable. Several serum markers, e.g. β_2 microglobulin, soluble CD23 and thymidine kinase, have been shown to predict progression and survival. Variations in predictor cut-off levels have limited their widespread application. Cytogenetic abnormalities are detected in >90% of cases. Patients with an isolated deletion at 13q have an excellent prognosis, in contrast to those with either 11q deletions or 17p deletions (the sites of the tumour suppressor genes *ATM* and *TP53* respectively) who tend to have a rapidly evolving clinical course. Trisomy of 12 is frequently observed and similarly conveys risk of progression. In those tumours that demonstrate a high level of mutation within the variable region of the rearranged immunoglobulin heavy chain (*IgVH*) the clinical course is more indolent than those where the *IgVH* sequence more closely resembles that of the germ line. Such assessments are technically demanding; expression of ZAP70, a 70 kDa tyrosine kinase protein, correlates well with mutational status. Patients with <20% expression of ZAP70 have median 10-year survival of ≥50%; in >20% expression the median survival was <5 years. High expression of CD38 on leukaemic cells may also indicate adverse prognosis.

Management

In CLL, the major consideration is when to treat, indeed 30% of patients will never require intervention. Treatment depends on the 'stage' (Table 9.15) of the disease and the prognostic biomarkers. Choice of therapy will depend upon patient-related factors such as age and co-morbidity, adverse prognostic features and anticipated response and toxicities to therapy. Intervention, when indicated, usually causes improvement in symptoms and in the blood count. The effect on survival is unclear. More aggressive treatments, particularly combinations of cytotoxic chemotherapy with antibody therapy, result in better quality remission of longer duration. These improvements may translate into a survival advantage, to accompany the improvement in quality of life afforded by good supportive care.

Early-stage disease is usually managed expectantly, advanced-stage disease is always treated immediately and the approach to the intermediate stage is variable. The absolute indications for treatments are:

- marrow failure manifest by worsening anaemia and/or thrombocytopenia
- recurrent infection
- massive or progressive splenomegaly or lymphadenopathy
- progressive disease manifest by doubling of the lymphocyte count in 6 months
- systemic symptoms (fever, night sweats or weight loss)
- presence of haemolysis or other immune mediated cytopenias.

General/supportive treatment

Anaemia due to haemolysis is treated with steroids. If it is refractory or recurrent, or if splenic discomfort is a problem, a splenectomy is performed. Anaemia and thrombocytopenia due to marrow infiltration is treated with chemotherapy and, when necessary, transfusion. Erythropoietin (see p. 390) may avoid the need for transfusions, particularly in patients receiving chemotherapy.

Infection is treated with antibiotics, with prophylactic therapy being given during periods of chemotherapy. Immunoglobulin replacement may be helpful.

Allopurinol is given to prevent hyperuricaemia.

Specific treatment

- Chlorambucil, given in modest doses, usually reduces the blood count and decreases lymphadenopathy and splenomegaly, and successfully palliates the disease. The bone marrow rarely returns to normal. Treatment is usually limited to a few months' duration and then withheld until progression. In asymptomatic patients without an indication for therapy, early use of chlorambucil does not provide a survival advantage over expectant management.
- *Purine analogues, fludarabine* alone or in combination with *cyclophosphamide* or *mitoxantrone* (with or without steroids), have had a much greater impact on the bone marrow and can induce complete or molecular complete remission although they are not helpful in 17p-deletion or p53 mutations.
- Combination therapy with *rituximab* (relatively ineffective alone) shows a dramatic improvement in the response rate and has become *standard choice first-line therapy*. Alemtuzumab, a humanized monoclonal antibody targeting CD52 which is highly expressed on B-CLL, may be used in those patients that progress after fludarabine.
- Allogeneic stem cell transplantation with non-myeloablative conditioning regimens is undergoing investigation, particularly for the younger patient.

Lymphomatous transformation

CLL may undergo lymphomatous (Richter's) transformation in 5–10% of cases, most typically to diffuse large B-cell lymphoma, although Hodgkin's like transformation is recognized. In the main, response to cytotoxic chemotherapy is unsatisfactory and survival short.

Hairy cell leukaemia (HCL)

HCL is a clonal proliferation of abnormal B (or very rarely T) cells which, as in CLL, accumulate in the bone marrow and spleen. It is a rare disease, median age at presentation is 52 years old and the male to female ratio is 4:1. The bizarre name relates to the appearance of the cells on a blood film and in the bone marrow – they have an irregular outline owing to the presence of filament-like cytoplasmic projections. They show a strong acid phosphatase reaction that is resistant to tartaric acid. The cells express many cellular differentiation markers including CD19, 20 and 103 but not CD21 or 5.

Clinical features

Clinical features include anaemia, fever and weight loss. Splenomegaly occurs in 80%, lymphadenopathy is uncommon. Anaemia, neutropenia, thrombocytopenia and low monocyte counts are found.

Treatment

The purine analogues 2-chloroadenosine acetate (2-CDA) (cladribine) and pentostatin have specific activity in this condition; complete remission is achieved in 90% with just one cycle of treatment. The remissions sometimes last for several years and patients can be retreated. Rituximab is used in cases who do not respond to the above drugs.

Prolymphocytic leukaemia

Prolymphocytic leukaemia is another rare disorder, often mistaken for CLL. It may be of B or of T cell lineage. It is characterized by bone marrow failure (anaemia, neutropenia and thrombocytopenia) and – as in HCL – splenomegaly. Treatment generally comprises chlorambucil as for CLL, although splenectomy may be indicated and fludarabine can be useful.

FURTHER READING

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THE LYMPHOMAS

The lymphomas are commoner than the leukaemias and are increasing in incidence for reasons which are unclear. They arise as the result of abnormal proliferation of the lymphoid system, and hence occur at any site where lymphoid tissue is found. Most commonly they are manifest by the development of lymphadenopathy at single or multiple sites, although primary extranodal presentations account for up to 20% of non-Hodgkin's lymphoma. The prognosis is determined by the specific subtype of lymphoma and the anatomical extent of disease and its bulk, the clinical course ranging from months to years.

The guiding principles of management are broadly the same as for the leukaemias. The precise diagnosis is established, appropriate further investigation is conducted to allow a management plan to be formulated, both for the short and long term, and the situation is clearly explained to the patient.

Lymphomas are currently classified on the basis of histological appearance into:

- Hodgkin's lymphoma
- non-Hodgkin's lymphoma.

The distinction between lymphoid leukaemia and lymphoma is not always clear.