Staging and general management

A Guide for Nurses

Leukaemia Care
Nurse Academy

Introduction

Discussion of the goals of treatment with the patient and family should, in most cases, focus on the potential benefits of treatment for short- and long-term outcomes.

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

In this booklet

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

Acute myeloid leukaemia

Induction therapy in AML generally comprises intensive combination chemotherapy to achieve a complete response (CR) by rapidly reducing the number of leukaemia cells and restoring normal bone marrow function. A CR is defined morphologically as fewer than 5% of blasts in a bone marrow aspirate, with the recovery of blood counts to normal. Post-remission therapy, including chemotherapy, targeted therapies, and autologous or allogeneic HSCT may be given to sustain the CR and achieve long-term disease-free survival. In the UK, most patients are offered access to a national clinical trial.

Induction therapy

Cytarabine/cytosine arabinoside (Ara-C)-based induction therapy is the standard of care for most patients with AML. Exceptions are patients with APML for whom disease-specific treatments, such as all-trans retinoic acid (ATRA) or arsenic trioxide, are required, and frail or elderly patients in poor health who may require lower-intensity regimens (see below). The standard treatment involves daunorubicin and Ara-C (DA) in regimens such as 'DA 3+7' or 'DA 3+10'. Patients are commonly hospitalised for several weeks while their blood cells recover, and complications of the disease and its treatment are managed.

In some centres, the initial response to treatment is evaluated with a bone marrow aspirate and biopsy 7 - 10 days after completion of induction chemotherapy to demonstrate adequate elimination of leukaemia cells reflected by bone marrow hypoplasia. Elsewhere, bone marrow examination is primarily performed to document the remission status after recovery of neutrophils and platelets, unless there is a prolonged delay to recovery.

Depending upon age, patient selection and various prognostic features, 60 80% of younger adults achieve a CR with such regimens, but only about one-third of patients overall are ultimately cured of AML. Some patients may need two courses of induction therapy to attain a CR.

CPX-351, a dual-drug liposomal encapsulation of DA, is approved

in the USA and Europe for the treatment of newly diagnosed therapy-related AML. A 5-year follow-up of a Phase III trial comparing CPX-351 with conventional DA 3+7 in older patients with high-risk/secondary AML reported significantly improved overall survival in those who received CPX-351, with a similar safety profile to that of conventional DA 3+7 treatment.

Post-remission therapy. Almost all patients who initially achieve CR ultimately relapse unless post-remission therapy is given. Post-remission therapy aims to eliminate any residual undetectable disease and achieve a cure. This may include two phases:

- consolidation therapy
- maintenance therapy

Consolidation therapy

Relatively intensive treatment given soon after achieving CR is generally described as remission consolidation therapy. It usually consists of one or more courses of chemotherapy (usually infusions of high-dose Ara-C [HiDAC therapy]), or autologous or allogeneic HSCT.

HSCT aims to restore haematopoietic function by the intravenous infusion of stem cells. HSCT may be autologous (derived from the patient's own tissues) or allogeneic (using cells derived from a donor).

For autologous HSCT, the patient should ideally have no demonstrable malignancy in the blood or bone marrow. Treatment-related morbidity and mortality are lower with autologous transplantation.

Allogeneic HSCT is the most potent way of reducing risk of relapse in patients with intermediate- or high-risk disease. Stem cell donors may be siblings or individuals unrelated to the patient (Figure 5.1). Success of the procedure depends on the degree of human leucocyte antigen (HLA) matching (also known as tissue typing) between donor and host; there are many HLA markers. Stem cells from umbilical cord blood do not require as much HLA matching as that from adult circulating blood.

Acute myeloid leukaemia (cont.)

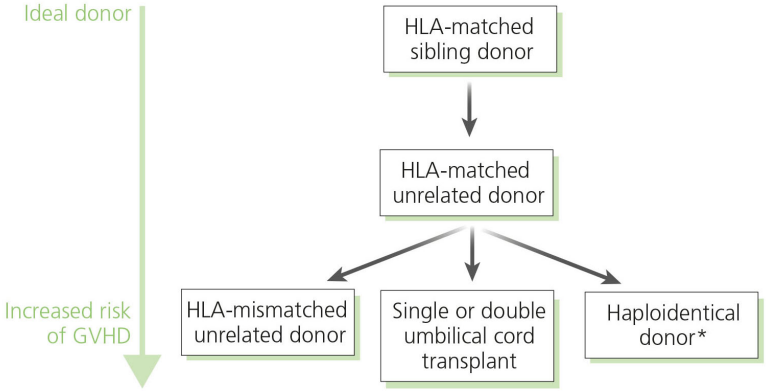

Figure 5.1 Stem cell sources for allogeneic HSCT by order of preference. The closer the HLA tissue type match between a donor and recipient, the less chance of transplant rejection and graft-versus-host disease (GVHD). *A haploidentical donor is a partial HLA match (usually about 50%) and may be a parent, sibling or child. Almost everyone has at least one haploidentical relative, so the chance of finding a donor is increased with a haploidentical transplant.

TABLE 5.1

Potential complications of HSCT

Early complications	Late-onset complications
• Bacteraemia or sepsis • Prolonged severe pancytopenia • Mucositis • Hepatic veno-occlusive disease • GVHD • Graft failure • Viral reactivation (CMV or EBV) • Haemorrhagic cystitis • Pulmonary complications • Transplantation-related thrombotic microangiopathy	• Chronic GVHD • Ocular effects • Endocrine effects • Congestive heart failure • Increased risk of malignancy • Late-onset infections

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

The likelihood of graft rejection and graft-versus-host disease (GVHD) are reduced in well-matched recipients. An ideal donor would be a sibling or unrelated donor who is completely matched at HLA-A, HLA-B, HLA-DR, HLA-C and HLA-DQ. As HLA mismatching increases so too does the risk of GVHD. The graft-versus-tumour effect that is integral to allogeneic HSCT (in which donor T cells eliminate residual malignant cells in the host) diminishes the chances of tumour relapse.

HSCs can be collected from bone marrow, peripheral blood or umbilical cord blood. Bone marrow has traditionally been the donor organ of choice; however, because of the invasive nature of the collection procedure, it has now been replaced by peripheral blood for all autologous transplants and a significant proportion of allogeneic transplants. Before collection, stem cells are mobilised with recombinant haematopoietic growth factors to boost stem-cell release into the blood.

Although HSCT is potentially curative, it is associated with several early and late-onset complications (Table 5.1). Indication for allogeneic HSCT is dependent on the balance of transplant-related mortality versus the benefit of reducing relapse risk.

Maintenance therapy

More prolonged lower-intensity therapy is described as remission maintenance therapy, which may continue for months to several years after CR. Recent maintenance strategies, including administration of the hypomethylating agents (DNA methyltransferase inhibitors) azacitidine (azacytidine) and decitabine, have been shown to improve clinical outcomes. The biggest advance in this area has been the approval of oral azacitidine, which has shown significant improvements in overall survival and relapse-free survival in patients with AML who have achieved remission after induction chemotherapy, with or without consolidation therapy.

Treatment of elderly or unfit patients. Overall outcomes are poor in elderly or unfit patients, and some are not referred for treatment because of serious comorbid conditions. Advanced age is commonly associated with poor outcomes due to both physical and biological factors. Older age is commonly associated with poor performance status and

Acute myeloid leukaemia (cont.)

organ impairments; moreover, elderly and frail patients are at increased risk of developing treatment-related complications. Elderly patients have a higher incidence of secondary AML and unfavourable cytogenetics, further leading to poor outcomes.

However, there is evidence that patients who are treated with low-intensity chemotherapy regimens survive longer than those who are not treated. Azacitidine and decitabine are often prescribed for elderly patients. They appear to offer better efficacy than current regimens in patients with unfavourable cytogenetics, suggesting their potential value in other difficult-to-treat patients with AML. Both agents are approved for the treatment of certain forms of AML. Nevertheless, a recent study of outcomes in older patients with AML treated with azacitidine and decitabine reported that, in real-world settings, a substantial proportion of patients did not receive standard dosing schedules and most did not complete the minimum recommended 4 cycles of treatment, thereby limiting response and survival benefits.

A recent advance in this area has been the approval of the B-cell lymphoma 2 (BCL2) inhibitor venetoclax, given in combination with hypomethylating agents or low-dose Ara-C. Venetoclax has produced promising results with a manageable safety profile in adults aged 75 years or older with newly diagnosed AML and those with comorbidities that preclude the use of intensive chemotherapy.

Glasdegib, a small-molecule inhibitor of the sonic hedgehog signalling pathway, combined with low-dose Ara-C, has also been approved for the treatment of this patient population.

Treatment of relapsed and refractory disease

Treatment decisions in patients with AML who have relapsed after induction therapy are influenced by the likelihood of attaining CR, comorbid illnesses (including active infections), the patient's eligibility for allogeneic HSCT and the availability of an HLA-matched donor. Refractory (resistant) disease is AML that fails to show a CR after one or two initial courses of induction therapy: resistance to induction

therapy is closely associated with unfavourable cytogenetic and molecular features and carries an unfavourable prognosis.

Allogeneic HSCT offers the highest likelihood of cure in patients with relapsed or refractory AML.

Targeted therapies

The presence of a targetable mutation can further guide treatment in patients with AML.

FLT3 inhibition

FLT3 mutations are present in approximately 30% of adults with newly diagnosed AML. Numerous oral FLT3-TKIs have been developed with variable pharmacokinetics and side-effect profiles.

Midostaurin is approved for use with standard DA induction therapy and HiDAC consolidation therapy, and for maintenance therapy in patients with a CR to induction therapy. In a randomised controlled trial, midostaurin's addition to standard induction and consolidation chemotherapy significantly improved overall survival and event-free survival, compared with standard treatment and placebo; this benefit was noted across differing FLT3 subtypes. Nevertheless, it is likely that midostaurin and intensive chemotherapy will be supplanted by second-generation FLT3-TKIs and novel combinations that incorporate these agents in the future. To date, gilteritinib has been approved as monotherapy in patients with relapsed or refractory FLT3-mutated AML. It is well tolerated and has been shown to improve outcomes compared with standard salvage chemotherapy.

IDH1 and IDH2 inhibition

Ivosidenib and enasidenib are oral selective small-molecule inhibitors of mutant IDH1 and IDH2 gene products, respectively. IDH1 and IDH2 mutations occur in 6–10% and 12% of patients with AML, respectively. In dose escalation and expansion studies, ivosidenib and enasidenib were well tolerated and provided durable remissions in patients with relapsed or refractory AML. However, a unique and potentially life-threatening adverse event associated with these agents is differentiation syndrome,

Acute myeloid leukaemia (cont.)

occurring in 4% of patients with ivosidenib and 7% of patients with enasidenib. At the time of publication, both agents had been approved in the USA, but not in Europe.

CD33 is expressed to some degree on the leukaemia blasts of all patients with AML. Gemtuzumab ozogamicin is a humanised anti-CD33 monoclonal antibody conjugated with calicheamicin, a potent anthracycline antibiotic. It is most effective in APML but induces remissions in other AML types as well and is approved for the treatment of adults with newly diagnosed, or relapsed or refractory, CD33+ AML. It is particularly effective in AML with core-binding factor translocations (involving chromosome 21). The indication for gemtuzumab ozogamicin was recently extended to paediatric patients in the USA.

Other novel therapies under evaluation for the treatment of AML include epigenetic therapies targeting both DNA and histone, agents that target specific antigens expressed on leukaemia blasts, antibody–drug conjugates, bispecific antibodies and novel inhibitors of the apoptosis pathway. Clinical trials are increasingly focusing on subgroups of patients with targetable mutations and those who are not eligible for standard intensive chemotherapy.

Acute lymphoblastic leukaemia

TABLE 5.2

Prognostic features in acute lymphoblastic leukaemia

Good prognosis	Poor prognosis
• No adverse cytogenetics • Age <30 years • WBC count < 30000/μL • Complete remission within 4 weeks	• Adverse cytogenetics, e.g. translocations t(9;22), t(4;11) • Age >60 years • Presence of precursor B-cell WBCs, with WBC counts >100000/μL • Failure to achieve remission within 4 weeks

Treatment of ALL is stratified according to patient age (<15 years old; 15 - 39 years; >39 years) and Philadelphia chromosome status (positive or negative). In general, ALL treatment consists of four components:

- induction therapy
- consolidation therapy
- maintenance therapy
- CNS prophylaxis

Treatment of adults

Approximately 20 - 40% of adults with ALL are cured using current treatment regimens. Principal factors that affect the prognosis are shown in Table 5.2.

Prognosis can also be affected by immunophenotype, chromosome number, MRD after treatment and recurrent genetic abnormalities.

Induction therapy

Standard induction therapy involves one of two regimens:

- vincristine, prednisone, an anthracycline and cyclophosphamide and/or L-asparaginase, given over 4–6 weeks
- the hyper-CVAD regimen (hyperfractionated cyclophosphamide and intensive doses of Ara-C and methotrexate, combined with dexamethasone

Acute lymphoblastic leukaemia (cont.)

and vincristine), possibly augmented with a TKI in patients who are positive for the Philadelphia chromosome, or rituximab in CD20+ patients.

The introduction of TKIs has revolutionised the treatment of Ph+ ALL, significantly improving prognosis. TKI monotherapy may lead to CR rates of 90–100%, even in older patients. The standard of care for fit patients is a combination of standard chemotherapy and TKI treatment (imatinib, dasatinib or ponatinib), which has led to longer disease-free survival in both adults and children. Clinicians should be aware that TKI treatment, mainly ponatinib, is associated with thrombosis and other, sometimes fatal, cardiovascular events.

Consolidation therapy

Regimens using the standard four- or five-drug induction protocol usually include consolidation therapy with Ara-C combined with an anthracycline or epipodophyllotoxin. Hyper-CVAD induction is consolidated with alternating cycles of high-dose methotrexate/HiDAC and hyper-CVAD.

Maintenance therapy consists of prednisone, vincristine, methotrexate and 6-mercaptopurine.

Central nervous system prophylaxis with intrathecal chemotherapy is essential in patients with ALL because meningeal involvement is a common finding at diagnosis. Intrathecal chemotherapy is based on methotrexate, which may be combined with hydrocortisone and Ara-C as necessary.

Haematopoietic stem cell transplantation

Most adults with ALL are offered allogeneic HSCT at first remission. HSCT can also be effective in patients who relapse, and it should be expedited after intensive salvage therapy.

Treatment of children

The prognosis of ALL is better in children than adults. Typically, children with ALL are assigned a risk status depending on several characteristics, including:

- age
- initial WBC count
- ALL subtype

- spread of disease
- chromosome number
- presence and type of translocations
- speed of initial therapeutic response

In general, children at higher risk are given more intensive therapy than those at lower risk. Several protocols for intensively managing paediatric patients have been devised. These generally aim to intensify doses of non-myelotoxic drugs such as prednisone, vincristine or L-asparaginase, to achieve improved therapeutic outcomes.

Induction therapy

Intensive treatments commonly used during induction therapy include dexamethasone or prednisone, vincristine, L-asparaginase and daunorubicin. A child with low-risk ALL may typically receive L-asparaginase, vincristine and a steroid such as dexamethasone as induction therapy, while a higher-risk patient would additionally receive methotrexate and/or 6-mercaptopurine.

Consolidation therapy often includes methotrexate and 6-mercaptopurine, or cyclophosphamide and Ara-C. Drugs used for intensification include Ara-C, cyclophosphamide, etoposide, dexamethasone, L-asparaginase, doxorubicin, methotrexate, 6-mercaptopurine and vincristine.

Maintenance therapy is based on oral 6-mercaptopurine daily, with oral methotrexate weekly and intravenous vincristine and steroids (prednisone or dexamethasone) as required.

Central nervous system prophylaxis

As in adults, intrathecal chemotherapy is based on methotrexate, which may be combined with hydrocortisone and Ara-C as necessary. Radiation therapy may be required in high-risk children, such as those with T-cell ALL, but this should be avoided wherever possible.

Haematopoietic stem cell transplantation

Children achieving first complete remission are offered allogeneic HSCT. HCST may also be offered to a select number of children

Acute lymphoblastic leukaemia (cont.)

who have a poor response to chemotherapy or relapsed disease.

Treatment of adolescents and young adults

Increasingly, more intensive paediatric-style treatment regimens are being used in adolescents and young adults with ALL. It has been proposed that the fundamental oncological changes underlying ALL in younger patients differ from those of older patients, making younger patients more resilient and amenable to more intensive therapeutic regimens. Clinical trials have shown paediatric regimens to be feasible and effective in this group. Risk factors for a poorer outcome included obesity and a BCR-ABL1-like gene expression signature.

Treating relapse

Patients with relapsed ALL have an extremely poor prognosis. If HSCT is not feasible, reinduction therapy using standard chemotherapeutic regimens, novel chemotherapeutic agents (clofarabine, nelarabine and liposomal vincristine) and immunotherapies (blinatumomab and inotuzumab ozogamicin) may be initiated either alone or in combination. Chimeric antigen receptor (CAR) T-cell therapy (tisagenlecleucel) may also be an option in relapsed patients with ALL.

Chemotherapeutics

Clofarabine is a purine nucleoside analogue, approved for treating relapsed or refractory ALL in children and young adults after at least two other types of treatment have failed. Nelarabine is the only agent approved for relapsed/refractory T-cell ALL following treatment with at least two other chemotherapy regimens. Liposomal vincristine (a sphingomyelin/cholesterol liposome-encapsulated formulation of vincristine) is approved for the treatment of patients with Ph+ ALL.

Immunotherapies

Blinotumomab is a bispecific T-cell engager, approved for the treatment of B-ALL in adults and children. It enables CD3+ T cells to recognise CD19, a protein that is expressed on the surface of most cancerous B cells, and destroy the leukaemia blasts. Blinotumomab

has been shown to significantly improve overall survival in this patient group compared with chemotherapy. Inotuzumab ozogamicin is an antibody–drug conjugate, that is, a humanised monoclonal antibody (inotuzumab) that targets CD22-expressing cells conjugated with the cytotoxic antibiotic calicheamicin. Upon binding, the complex is internalised within the leukaemia cell and the calicheamicin is released causing cell death. It is approved for the treatment of adults with CD22+ relapsed/refractory B-ALL. It has also been studied in Ph+ ALL with positive results.

CAR T-cell therapy

Autologous T cells are harvested from peripheral blood and genetically engineered to produce a CAR that targets CD19. Once expanded, the engineered T cells are reinfused into patients who have undergone lymphodepleting chemotherapy (Figure 5.2). Tisagenlecleucel is a CD19-directed CAR T-cell immunotherapy, indicated for patients under 25 years of age with B-cell ALL who are in or have had two or more relapses, or are refractory to other treatments.

Most patients experience CAR T-related adverse events, including cytokine release syndrome and neurological toxicity.

Treating BCR-ABL1-like ALL

Several clinical trials are under way to determine if TKIs are effective in BCR-ABL1-like ALL, since in vitro and ex vivo data suggest that leukaemia cells expressing various genetic abnormalities are specifically sensitive to individual TKIs. Treatment with immunotherapies and CAR T-cell therapies are also being evaluated in these patients.

Future directions

Efforts are being made to optimise both frontline and relapsed/refractory therapeutic options, for example by combining targeted agents with lower-intensity chemotherapy. Further molecular targets are also being explored.

Acute lymphoblastic leukaemia (cont.)

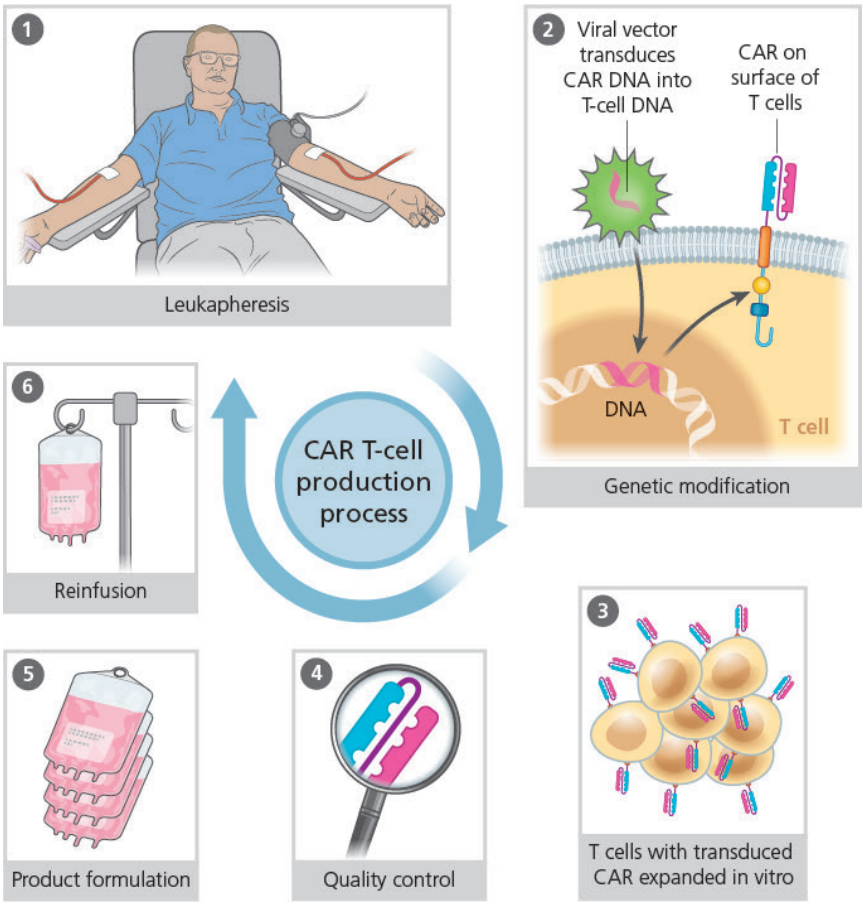

Figure 5.2 CAR T-cell therapy. (1) T cells are collected from the patient by leukapheresis, (2) genetically modified ex vivo to carry the CAR, (3) cultured, and (4,5) tested for CAR T-cell proportion and cell viability. (6) The CAR T cells are then reinfused into the patient who, in the meantime, has undergone conditioning with lymphodepleting chemotherapy.

Chronic myeloid leukaemia

Staging and how to treat

The natural history of CML consists of three distinct phases, each of which requires a different approach to treatment.

- Chronic stable phase, a relatively indolent condition that is easily controlled with oral agents.
- Accelerated phase, a more aggressive disorder (Table 5.3) in which disease control is more difficult to achieve.
- Blast (crisis) phase (Table 5.4), most long-term survivors are those who have received HSCT.

Improvements in the management of chronic stable disease in recent years have resulted in fewer patients (approximately 6% at 5 years) progressing to the accelerated or blast phases of the disease.

Treatment options

TKI treatment for patients with CML has been revolutionary. Other methods of disease control include allogeneic HSCT or palliative therapy with cytotoxic agents. Multiple factors will influence the choice of therapy in CML, including:

- the phase of CML
- the response to treatment with TKIs (for patients in early phases)
- age
- availability of a donor for HSCT
- medical comorbidities affecting suitability for HSCT

Tyrosine kinase inhibitors

Oral TKIs include imatinib, dasatinib, nilotinib, bosutinib and ponatinib. These agents target the constitutively active tyrosine kinase implicated in the pathogenesis of CML. Although they may not cure the disease, they can achieve long-term control of CML in most patients; as a result, they have become the initial treatment of choice for almost all newly diagnosed patients with CML.

Chronic phase

Imatinib was the first TKI approved for patients with chronic-phase CML, but data from randomised trials in

Chronic myeloid leukaemia (cont.)

TABLE 5.3

Criteria for accelerated phase in CML

One or more of the following:
• 10 - 19% blasts in the peripheral blood or bone marrow
• Peripheral blood basophils ≥20%
• Platelets <100000/µL, unrelated to therapy
• Platelets >1000 000/µL, unresponsive to therapy
• Progressive splenomegaly and increasing WBC count, unresponsive to therapy
• Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia chromosome)

TABLE 5.4

Criteria for blast phase in CML

One or more of the following:
• ≥20% peripheral blood or bone marrow blasts
• Large foci or clusters of blasts on bone marrow biopsy specimen
• Presence of extramedullary blastic infiltrates (e.g. myeloid sarcoma, also known as granulocytic sarcoma or chloroma)

newly diagnosed patients have shown that more potent, second-generation (dasatinib, nilotinib and bosutinib) and third-generation (ponatinib) TKIs produce faster and deeper responses than imatinib. However, these randomised trials comparing imatinib with newer TKIs have not demonstrated improvements in overall survival. Long-term data show that the responses to imatinib have been very durable, with rates of progression being lower in successive years and with very few relapses after 3 - 4 years of follow-up. In addition, thrombocytopenia, cardiovascular events, and pancreatic and hepatic effects are more frequent among patients treated with the newer TKIs, making imatinib a better option for patients with comorbidities.

A small proportion of previously untreated patients with chronic-phase CML are resistant to or intolerant of treatment with TKIs (patients who develop the T315I mutation are resistant to all TKIs except ponatinib). In addition, some patients with initial responses to a TKI ultimately lose their response. Hence, careful follow-up is critically important to predict when other therapies, such as alternative TKIs or transplantation, should be considered. The response to therapy is monitored periodically with blood counts, bone marrow biopsy and PCR assay of the peripheral blood.

Numerous studies have shown that about 50% of patients who have maintained a major molecular response (MMR) – BCR–ABL up to 0.1% in the blood – for at least 2 years are able to stop TKI treatment and remain relapse-free for 3 years or more. In a 6-year follow-up of patients in the European Stop Kinase Inhibitor (EURO-SKI) study, 10.8% of patients lost MMR at a median of 51 months after stopping treatment. Molecular status at 3 years after TKI discontinuation was found to be highly predictive of subsequent relapse. There is always the possibility that the disease will recur, although this becomes less likely the longer treatment-free remission continues, so careful long-term monitoring is required. In patients who relapse, it is possible for a molecular response to be achieved again if the same TKI,

Chronic myeloid leukaemia (cont.)

or a different TKI, is started. All relapsed patients who restarted TKI therapy in the EURO-SKI study regained MMR within 1–5 months. No patients progressed to the accelerated or blast phases of the disease.

Accelerated or blast phase

The prognosis for CML in the accelerated or blast phase is dismal, particularly for patients previously treated with a TKI, as these phases tend to be relatively resistant to most forms of treatment. Responses are short lived, although responding patients survive longer than non-responders. There is a significant relapse rate in patients in the accelerated or blast phase even after successful treatment with TKIs, and it is appropriate to consider transplantation in such individuals. As such, a reasonable plan is to initiate a search for a matched donor while attempting to return the patient to a second chronic phase, during which suitable candidates can subsequently undergo transplantation. The use of TKIs in the post-transplant setting has resulted in an apparent reduction in relapse risk.

Haematopoietic stem cell transplantation is used in the management of several types of leukaemia. In patients with CML, potential indications include non-responsiveness to TKIs, relapse, and atypical or high-risk features.

Other agents that may be beneficial in patients who are not transplantation candidates and are intolerant or refractory to treatment with TKIs include hydroxyurea, IFN with or without Ara-C, azacitidine, decitabine, busulfan and omacetaxine mepesuccinate. Asciminib (ABL001) is an agent in development for the treatment of Ph+ CML. It works in a different way to the existing TKIs: instead of binding to the ATP site of the BCR-ABL1 oncoprotein, it makes it change shape, disabling it so that it no longer works. Recent results from a Phase III trial have shown clinical efficacy for patients with recurrent chronic phase CML despite two previous courses of TKIs.

Chronic lymphocytic leukaemia

Staging and when to treat

There are two main staging systems for CLL. The Rai staging system divides the disease into five stages; it is most used in the USA. The Binet staging system divides the disease into three stages and is the preferred system in Europe (Table 5.5). CLL is an extremely heterogeneous disease, with certain subsets of patients having survival rates without treatment that are similar to the normal population. Hence, not all patients with CLL will require treatment at the time of diagnosis.

Asymptomatic early-stage disease

Although highly variable, patients with asymptomatic early-stage CLL (Rai stage <3; Binet stage A or B) have a median survival greater than 10 years. Observation rather than immediate treatment is the standard of care for newly diagnosed patients with early-stage asymptomatic CLL. Early initiation of chemotherapy has failed to show benefit and may even increase mortality.Localised radiotherapy is usually offered to patients with localised (stage I) CLL.

Symptomatic or advanced-stage disease

In contrast, patients with more advanced CLL, or those with symptoms or progressive disease, have a median survival of 18 months to 3 years without treatment. Treatment of the underlying CLL is indicated for patients who develop disease-related symptoms or evidence of progressive disease ('active disease'), and this can improve median survival to approximately 5 - 8 years.

Pretreatment evaluation

The following studies should be performed before initiating treatment in patients with CLL:

- laboratory studies, including complete and differential blood counts, and clinical chemistry evaluations (liver and renal function, electrolytes, alkaline phosphatase, lactate dehydrogenase, β2-microglobulin and direct antiglobulin tests)
- testing for HIV, hepatitis B and

Chronic lymphocytic leukaemia (cont.)

TABLE 5.5

Staging systems for CLL

Rai stage	
0 (Low risk)	• Lymphocytosis; no enlargement of lymph nodes, spleen or liver • Near-normal RBC and platelet counts
I (Intermediate risk)	• Lymphocytosis + enlarged lymph nodes; no enlargement of spleen or liver • Near-normal RBC and platelet counts
II (Intermediate risk)	• Lymphocytosis + enlarged spleen (possibly an enlarged liver) ± enlarged lymph nodes • Near-normal RBC and platelet counts
III (High risk)	• Lymphocytosis + anaemia ± enlarged lymph nodes, spleen or liver • Near-normal platelet count
IV (High risk)	• Lymphocytosis + thrombocytopenia ± anaemia, enlarged lymph nodes, spleen or liver

Binet stage	
A	• <3 areas of lymphoid tissue* enlarged • No anaemia or thrombocytopenia
B	• ≥3 areas of lymphoid tissue* enlarged • No anaemia or thrombocytopenia
C	• Anaemia and/or thrombocytopenia present

*Neck lymph nodes, groin lymph nodes, underarm lymph nodes, spleen and liver.

hepatitis C

- unilateral bone marrow aspirate and biopsy for all patients who have cytopenias of unknown cause
- evaluation of the peripheral blood with FISH for del(17p), del(11q), trisomy 12, del(13q) and t(11;14), to determine appropriate treatment regimens and rule out mantle cell lymphoma
- chest radiograph to identify hilar and mediastinal lymphadenopathy

CT of the chest, abdomen and pelvis is not required before treatment; it is usually reserved for patients enrolled in clinical trials. However, a CT should be performed in any patient in whom enlarged abdominal or pelvic nodes are suspected as a result of complications such as obstructive jaundice, or obstruction of the inferior vena cava or ureters.

Disease-related complications that warrant therapy are listed in Table 5.6.

Lymphocytosis itself, even if extreme, is not a strict indication for treatment if patients have no symptoms and adequate bone marrow function. The trend in lymphocyte count, and its effect on the patient, is more important than the absolute lymphocyte number. Clinical examination and blood counts at 3-monthly intervals for 12 months will enable a clear decision to be made as to whether the patient has aggressive disease or not. Lymphocyte doubling time (the time it takes for the lymphocyte count to double; LDT) is a simple parameter that can be useful in the clinical management of CLL. A high LDT indicates a good prognosis, while a lower LDT is associated with more rapid disease progression (see Table 5.6), which may require treatment.

Treatment options

The aims of treatment in patients with symptomatic CLL are to ameliorate symptoms and improve progression-free and overall survival: with the possible exception of allogeneic HSCT, current treatment options for CLL are not curative.

Immunochemotherapy

There is no standard frontline treatment regimen for patients with symptomatic CLL: a

TABLE 5.6

Disease-related indications for therapy for CLL
• Symptoms such as weakness, night sweats, weight loss, fever, progressive increase in the size of lymph nodes, or pain associated with enlarged lymph nodes
• Symptomatic anaemia and/or thrombocytopenia* (Rai stages III or IV; Binet stage C, see Table 5.5)
• Autoimmune haemolytic anaemia and/or thrombocytopenia that is inadequately responsive to corticosteroid therapy
• Progressive disease, defined as increasing lymphocytosis with a lymphocyte doubling time of <6 months, and/or rapidly enlarging lymph nodes, spleen and liver†
• Repeated episodes of infection‡

*Autoimmune-mediated anaemia or thrombocytopenia is treated with therapy directed at the autoimmune process before treatment of the underlying CLL is initiated.

†Transient localised lymphadenopathy in response to localised infections is not necessarily an indication for initiating treatment.

‡Hypogammaglobulinaemia without repeated episodes of infection is not a clear indication for therapy.

TABLE 5.7

Treatment regimens for CLL*
• Fludarabine, cyclophosphamide and rituximab
• Fludarabine and rituximab
• Fludarabine, cyclophosphamide and mitoxantrone
• Pentostatin, cyclophosphamide and rituximab
• Cyclophosphamide, vincristine and prednisone†
• Cyclophosphamide, doxorubicin, vincristine and prednisone
• Bendamustine†
• Ibrutinib ± obinutuzumab or rituximab
• Acalabrutinib ± obinutuzumab
• Idelalisib and rituximab
• Venetoclax ± obinutuzumab

*Other drugs or combinations of drugs may also be used. †Sometimes with rituximab.

Chronic lymphocytic leukaemia (cont.)

wide variety of chemotherapy regimens are used, often combining nucleoside analogues (for example, fludarabine), alkylating agents (for example, cyclophosphamide) and biological agents (for example, rituximab). Choice of treatment will depend on the person's age, disease risk and symptoms, as well as prognostic factors such as chromosome 17 or 11 deletions. Common treatment regimens are shown in Table 5.7; these may be used as first- or second-line options.

Younger patients who receive FCR have longer progression-free survival than those who receive bendamustine and rituximab (BR). However, this is not the case in patients aged over 65 years, and for those in this age group who are not eligible for ibrutinib (see below), BR is the preferred option. The anti-CD20 monoclonal antibody obinutuzumab is approved for several indications in CLL. A large multicentre trial is under way, comparing obinutuzumab monotherapy with its use in combination with fludarabine/cyclophosphamide, chlorambucil or bendamustine. It may be that obinutuzumab eventually replaces rituximab in the FCR regimen.

Bruton's tyrosine kinase inhibitors

Ibrutinib is an oral covalent inhibitor that binds to BTK, preventing its kinase activity, leading to the apoptosis of CLL cells. It is approved for use in both previously treated and untreated patients with CLL, and is used as primary treatment in patients with chromosome 17p13.1 deletions or TP53 mutations and in whom immunochemotherapy is unsuitable. Ibrutinib can also be given in combination with BR or with obinutuzumab or rituximab.

Acalabrutinib is a more selective BTK inhibitor than ibrutinib and has exhibited a good safety and efficacy profile in patients with relapsed CLL. Acalabrutinib monotherapy can be given to patients with symptomatic CLL who have been previously treated, and on its own or in combination with obinutuzumab to previously untreated patients.

Phosphatidylinositol 3-kinase inhibitors

Idelalisib is a potent selective

Chronic lymphocytic leukaemia (cont.)

inhibitor of PI3K, inducing CLL cell death while leaving T and NK cells unaffected. It is approved for use in relapsed CLL in combination with rituximab and can be given to patients with poor prognostic factors.

BCL2 inhibition

Venetoclax is a highly selective inhibitor of BCL2, a protein essential for CLL cell survival. Early trials of venetoclax showed an overall response rate of 70–80%, including in patients with a 17p deletion or TP53 mutation in whom it can be given as monotherapy. Venetoclax can also be given in combination with ibrutinib, obinutuzumab or rituximab. The first-line oral combination of venetoclax and ibrutinib has been shown to produce complete remission, including undetectable MRD, after 12 cycles, without the need for further treatment.

B-cell prolymphocytic leukaemia

B-PLL is commonly treated with combination regimens used for CLL (see Table 5.7). Individual chemotherapy regimens have not been directly compared, and the choice of regimen is largely made based on the side-effect profile and the clinician's experience with the regimen. Survival is usually 3–5 years despite therapy.

Hairy cell leukaemia

Pre-treatment evaluation of patients with HCL must establish the precise diagnosis, the extent of disease and the performance status of the patient. Particular attention should be paid in the history and physical examination to palpable enlargement of the spleen, liver and/or lymph nodes, and history of recent infections.

While not curative, modern therapy for HCL can alleviate symptoms, reverse cytopenias and prolong survival to near normal. In most patients, durable remissions can be achieved, with long treatment-free periods followed by further therapy after symptomatic relapse.

When to treat

Many patients with HCL are asymptomatic and can be observed for months or years before requiring treatment. Therapy is indicated only when the patient develops one or more of the following:

- significant cytopenias (for example, absolute neutrophil count <1000/µL, haemoglobin concentration <11g/dL or platelet count <100000/µL)
- symptomatic splenomegaly (common) or symptomatic lymphadenopathy (uncommon)
- constitutional symptoms such as fever, night sweats, fatigue or weight loss

Treatment may also be appropriate for patients with less-severe cytopenias that are symptomatic (for example, repeated infections and bleeding) and for those with progressive lymphocytosis.

Treatment options

Purine analogues, such as cladribine or pentostatin, are the preferred initial treatment for most patients with symptomatic HCL and normal renal function. Durable responses are seen in more than 90% of patients, with a median progression-free survival of 9 11 years. Splenectomy may be offered as a palliative therapy in patients with symptomatic splenomegaly (massive enlargement, pain, infarction and rupture), as a temporising measure in symptomatic pregnant women, or as a salvage therapy in patients with persistent pancytopenia despite therapy.

Immediately after treatment, patients should be monitored with serial complete blood counts to assess count recovery, and evaluated for fever and signs or symptoms of infection. Response should be formally assessed 4 6 months after the conclusion of primary therapy.

IFNα may be the preferred initial treatment in patients with severe pancytopenia, active infection or both, to improve blood counts and allow for subsequent therapy with purine analogues. IFNα may also be used for patients treated unsuccessfully with purine analogues. IFNα may also be the preferred option for patients with HCL who require treatment during pregnancy, although most pregnant patients will be able to postpone therapy until after delivery.

Key points – staging and general management

- Induction therapy for most patients with AML comprises intensive cytarabine/anthracycline-based chemotherapy aimed at achieving a CR. However, almost all patients who achieve a CR after induction therapy will ultimately relapse without post-remission therapy. This comprises one or more courses of chemotherapy, or allogeneic HSCT, given to eliminate any residual disease and achieve a cure.
- Maintenance therapy with oral azacitidine or decitabine has been shown to improve clinical outcomes in AML. These agents are also often prescribed for elderly patients who are ineligible for high-intensity chemotherapy regimens.
- The BCL2 inhibitor venetoclax, given in combination with azacitidine or low-dose Ara-C, has shown clinical efficacy and a manageable safety profile in adults aged 75 years and older with newly diagnosed AML.
- Identifying genetic mutations can further guide targeted treatment in patients with AML.
- Treatment for ALL comprises chemotherapeutic induction, consolidation and maintenance therapy with CNS prophylaxis, followed by HSCT.
- Patients with relapsed ALL have a very poor prognosis. Treatment options include novel chemotherapeutics, immunotherapies and CAR T-cell therapy.
- Treatment options for patients with CML include disease control with TKIs or palliative therapy with cytotoxic agents, and less commonly HSCT. TKIs are the initial treatment of choice for almost all patients with newly diagnosed CML.
- Treatment decisions for patients with CML depend on the phase of the disease, response to TKI treatment, the patient's age and eligibility for HSCT.

- The standard of care for patients with newly diagnosed CLL is observation rather than immediate treatment. Treatment is indicated for patients with more advanced or symptomatic disease. Small-molecule inhibitors are revolutionising the treatment of CLL.

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

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