

Leukaemias & Lymphomas

What is leukaemia, what is lymphoma?

Leukaemias and lymphomas are cancers of white blood cells. Leukaemias are characterised by malignant cells predominantly in the bone marrow and blood while lymphomas involve clusters of malignant lymphocytes in lymph nodes and other areas of the human body. Chronic leukaemias may progress slowly over years, but acute leukaemias are much more aggressive and often lead to death within months, or even weeks.

Leukaemias are subdivided according to the cell type affected. Examples are acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML). CML may convert into an acute form, a process known as blast transformation or blast crisis, which is notably therapy-resistant.

Related malignant diseases of the blood cells and lymphoid tissue include multiple myeloma, myelodysplastic syndrome (MDS), Hodgkin's disease and non-Hodgkin's lymphoma (NHL).

Chronic forms of leukaemia cause symptoms such as a tendency to recurrent infections, fatigue and various signs of immune deficiency. In acute leukaemia, there is an imbalance in the ratio of blood cells owing to infiltration of bone marrow. Symptoms may include weakness, fatigue and shortness of breath due to anaemia, severe infections, bleeding and bruising due to decrease of blood platelets, bone pain and enlargement of organs such as liver, spleen and lymph nodes.

Who does leukaemia and lymphoma affect?

Acute leukaemias occur in children and adults, whereas chronic leukaemias are uncommon under the age of 50. Each year, about 165,000 people in Europe are diagnosed with some type of blood or lymphoid malignancy, about 42,000 of them with leukaemias (5,000 cases in children) and 59,000 with lymphomas (4,000 cases in children). NHL is the most common blood cancer (about 50,000 cases per year) and some are associated with HIV infection.

Present treatments:

Leukaemias and lymphomas are generally more successfully treatable with medicines than most cancers, although remission rates vary considerably from one type to another. In many cases, life expectancy is now much increased. Two main approaches are used: (i) conventional (cytotoxic) anti-cancer agents, possibly supported by therapy with naturally occurring proteins called cytokines e.g. interferon or granulocyte colony-stimulating-factor (G-CSF), and (ii) bone marrow transplantation.

A variety of combination chemotherapy regimens have been developed that can achieve good remission rates, but no 'standard' therapies are recognised; instead,

Leukaemias and lymphomas are cancers of white blood cells. Treatment with medicines and bone marrow transplantation has greatly improved the survival and quality of life for people with these conditions. Further advances – including the use of antibodies to target therapy – offer the hope of continued improvements in therapy.



specialised cancer centres are constantly refining treatment procedures. Ten-year survival for all kinds of childhood leukaemias has risen from just over 20 per cent in the mid 1960s to around 70 per cent today.

More than 80 per cent of children with ALL, the most common type, are alive five years after diagnosis and treatment, whereas in 1960 they only lived for about four months after diagnosis. Eventual relapse remains a problem, due to the difficulty of eliminating all the malignant cells. The therapy of adult patients with ALL remains challenging. In general, treatment is following the protocols that have been developed to treat paediatric ALL.

For the treatment of CLL, chemotherapeutic agents are combined with monoclonal antibodies (mAbs) that bind to the surface of malignant white blood cells. Commonly used compounds include alkylating agents and a fluorinated nucleoside analogue.

The conventional approach to treat AML is based on a combination of an anthracycline and a nucleoside analogue. A new compound for the treatment of AML consists of a humanised mAb coupled to a cytotoxic antibiotic. The mAb half of the molecule binds to an antigen which is expressed on the surface of the leukaemic cells in AML, accurately targeting the medicine to its intended goal, with the intention of maximising effectiveness and minimising side-effects. The first dioxolane nucleoside anticancer agent is also available as first-line therapy in AML.

Particular excitement has been generated by a new medicine for CML which is an inhibitor of tyrosine-kinase. The mechanism of action is the inhibition of exchange of information between chromosomes 9 and 22 ("Philadelphia chromosome"). This therapy results in long-lasting remissions, but bone marrow transplantation remains the only curative treatment.

In patients with MDS, treatment is directed towards preventing infectious diseases and reducing the need for transfusions. In 2003, a compound received orphan drug designation in the EU for the treatment of MDS. For the therapy of relapsed or refractory multiple myeloma a proteasome-inhibiting compound is available for patients who have received previous therapies and have demonstrated disease progression on the last therapy. The principle of proteasome inhibition has been shown to lengthen the time before relapse and to extend survival to 80 per cent survival at one year, compared with the previous standard treatment with high-dose corticosteroids.

Side-effects of cytotoxic drugs such as vomiting and bone marrow suppression may limit the dose that can be used, but newer anti-emetics and G-CSF can minimise these problems in many cases.

What's in the development pipeline?

Many new agents are being developed for the various types of leukaemia and lymphoma and only a limited number of selected medicines can be discussed here.

There is a marked need for new treatments of AML. The theory behind new compounds for the treatment of AML is targeting FLT kinase, which is activated by a mutation in the FLT gene in about 30 per cent of AML patients. This receptor activation has been linked to cases of AML with a particularly poor prognosis.

Current therapies cure AML in fewer than 10 per cent of patients with the mutation. Clinical research has been expanded to evaluate the new molecules in different doses and in AML patients with normal FLT genes. Long-term plans include using the molecule in combination with standard chemotherapy for AML.

In CML, the problem of emerging resistance limits long-term survival and new treatments are still needed. Other antagonists of tyrosine kinase are in advanced development.

CLL often progresses slowly and fewer patients are given chemotherapy than in acute leukaemias. However, those with anaemia or thrombocytopenia, i.e. low platelet counts, often have a poorer prognosis and may be given treatment with cytotoxic medicines. There are currently few treatment options for those who become resistant to conventional therapy.

Therefore, development is ongoing to find out whether a specific inhibitor of protein C kinase could be used for this purpose. Another principle targeting CLL consists of inhibiting the production of Bcl-2, a protein made by cancer cells. Bcl-2 is thought to block chemotherapy-induced cell death, so the compound enhances the effectiveness of current anticancer treatments.

Another approach to treat CLL patients is an intravenously-given fluorinated nucleotide. Refractory CLL is also the target for a monoclonal antibody that is directed against an antigen on malignant lymphocytes.

A monoclonal antibody is also providing a new therapy in NHL, the most frequent lymphoid malignancy. NHL is classified into many different sub-types, according to the cells that each arise from, and these may vary in their response to therapy. The mAb is directed against antigens on the malignant B-cells in NHL and acts as a vehicle for radioactive iodine to deliver localised radiation therapy.

A further mAb, currently in Phase 3 development, is being investigated for use in follicular lymphoma in patients that no longer respond to other treatment. Also in Phase 3 are cytotoxic molecules which can be given orally and are designed to facilitate stem cell transplantation. Phase 2 compounds include further mAbs and combinations with cytotoxic compounds or interleukin-2.

The longer-term future:

Advances in treating leukaemias and lymphomas are typically made in incremental steps, but recently new medicines, cytokine therapy and bone marrow transplantation have combined to make a very real impact, especially in children, for whom survival prospects are now greatly improved.

MABs offer valuable opportunities for targeting cytotoxic drugs to their greatest effect so that side-effects are minimised and a continuing refinement of chemotherapy seems likely to continue.

Given the large number of new compounds in the Phase 2 and Phase 3 pipeline, the outlook for improved and better-tolerated therapies for this diverse group of malignant diseases is encouraging.

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