**CANCER 15**

**Cancer as a disease - LEUKAEMIA**

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**LEARNING OBJECTIVES**

The student should be able to

* Explain what “leukaemia” is
* Explain the difference between lymphoid and myeloid leukaemias and between acute and chronic leukaemias
* Outline the clinical and haematological features and representative cytogenetic and molecular genetic abnormalities of acute lymphoblastic leukaemia

“Leukaemia” was first described, almost simultaneously, in Edinburgh and Berlin, in 1845. The striking abnormality that was noted when the blood was examined after the patients’ deaths was the increase of “white corpuscles” in the blood. This gave rise shortly afterwards to the term “leukaemia”, derived from the Greek words for “white” and “blood”. We now know that leukaemia is essentially a bone marrow disease and overspill of the abnormal cells into the blood, producing “white blood”, is not essential for this diagnosis.

Leukaemia is a neoplasm or cancer arising as a result of mutation in a precursor of myeloid or lymphoid cells. In this context, “myeloid” may include not only the precursors of granulocytes and monocytes but also cells of erythroid and megakaryocyte lineages. Leukaemia differs from many other cancers in that haemopoietic and lymphoid stem cells usually circulate in the blood stream and migrate into various tissues. Mature lymphocytes, granulocytes and monocytes also normally enter tissues. It is difficult to apply the concepts of local invasion and metastasis to populations of cells that are normally mobile. The formation of localized tumour masses is also not inevitable in leukaemia, at least not in the earlier stages of the disease. We have to look at other characteristics of this disease to understand that leukaemia is a type of cancer.

The terms “malignant” and “benign” are not usually applied to leukaemias. However there are two terms that describe the clinical behaviour of different types of leukaemia that show a greater or lesser degree of malignancy; these are “acute and “chronic”. They describe the natural history of leukaemia in the absence of effective treatment.

An acute leukaemia is one that, if untreated, has profound pathological effects and leads to death in a matter of days, weeks or months.

A chronic leukaemia is one that causes less impairment of function of normal tissues and, although it will eventually lead to death, this usually does not occur for a number of years. Leukaemias can thus be acute or chronic, lymphoid or myeloid, permitting an oversimplified classification, which will suffice for our purposes.

**Table 1**

|  |  |  |
| --- | --- | --- |
|  | **Acute** | **Chronic** |
| Lymphoid | Acute lymphoblastic leukaemia | Chronic lymphocytic leukaemia |
| Myeloid | Acute myeloid leukaemia | Chronic myeloid leukaemia |

Leukaemia results from a number of mutations occurring in a primitive cell that, as a result, has a growth or survival advantage over normal cells that have not undergone mutation. That single cell gives rise to a clone that steadily replaces normal cells. The mutations concerned are in proto-oncogenes (also known as oncogenes) and sometimes also in tumour suppressor genes.

The types of mutations in oncogenes known to contribute to leukaemias include:   
(i) point mutations;  
(ii) internal tandem duplication of parts of genes;  
(iii) formation of fusion genes;  
(iv) dysregulation when a gene comes under the control of the promoter or enhancer of another gene;  
(v) somatic hypermutation subsequent to a translocation.

In addition, gene expression may be abnormal as a result of demethylation.   
The types of changes that can occur in tumour suppressor genes include deletion of the gene and inactivation through mutation. The abnormal behaviour of the leukaemic clone may include growth that occurs without a dependence on growth factors, continued proliferation without maturation, and a failure to undergo normal cell death or apoptosis.

Why does leukaemia occur? Mutations occur in human genes. Mutations in germ cells may be beneficial, neutral or harmful; beneficial germline mutations permit the species to evolve. Mutations in somatic cells are rarely useful. They may be neutral or positively harmful, in the latter case sometimes the cell just dies but sometimes the mutation leads to leukaemia or other cancer. Sometimes there is an identifiable cause (Table 2) but often no specific cause can be identified and yet mutation has occurred and leukaemia has developed. This process of mutation in a somatic cell may be the result of undetected exposure to mutagens or it may be a random, spontaneous process. The older a person is the more likely it is that enough spontaneous or induced mutations to have accumulated in a single cell for the cell to expand into a clone, replacing normal cells and behaving in a ‘malignant’ manner.

Acute myeloid leukaemia that occurs in late middle and old age can often be demonstrated to be the result of multiple sequential mutations. Leukaemia may thus be, in part, the result of spontaneous mutations—an inevitable feature of our ability as a species to change and evolve—and, in part, a consequence of exposure to environmental mutagenic influences that increase the rate of mutation considerably above the natural baseline rate.

Somatic mutation starts well before birth, many cases of leukaemia in infants now being known to result from intra-uterine events. In the case of B-lineage lymphoid leukaemias, antigenic stimulation may also be relevant to leukaemogenesis. This normally leads to rearrangement of DNA so that antibodies of greater affinity are produced. If the process goes wrong, a lymphoid stem cell could acquire a malignant phenotype. There is circumstantial evidence for this in the case of B-lineage acute lymphoblastic leukaemia (and also some B-lineage lymphomas).

**Table 2 Causes of leukaemia**

|  |  |
| --- | --- |
| Acute lymphoblastic | Usually unknown, sometimes mutagenic drugs or exposure to irradiation or chemicals *in utero*; possibly delayed exposure to a common pathogen or pathogens |
| Acute myeloid | Usually unknown, sometimes irradiation or mutagenic drugs or chemicals (benzene, cigarette smoke) |
| Chronic myeloid | Usually unknown, rarely irradiation or mutagenic drugs |
| Chronic lymphoid | Unknown but some families are predisposed |

The signs and symptoms of leukaemia mainly result from:

(i) proliferation of abnormal cells, e.g. bone pain, hepatomegaly, splenomegaly and lymphadenopathy (the latter mainly in lymphoid leukaemias)

(ii) loss of function of normal tissues as a result of replacement by leukaemic cells, e.g. loss of bone marrow function leading to anaemia, thrombocytopenia, neutropenia

Obviously, it is the nature of mutations that determines whether a leukaemia is acute or chronic. Acute leukaemias often result from mutation in genes encoding transcription factors with a resultant profound abnormality in the cells ability to mature. However the cells continue to proliferate so that there is an accumulation of primitive cells referred to as blast cells, either lymphoblasts of myeloblasts, as the case may be.

In chronic myeloid leukaemias the mutations often involve constitutive activation of signalling pathways within the cell. Cells can proliferate without needing growth factors. Interaction with stroma may be abnormal and cell survival may be prolonged so that there is a steady expansion of the leukaemic clone. However maturation still occurs and, in the case of myeloid cells, mature end cells are still able to function. The impairment of normal physiological processes is therefore much less than in the acute leukaemia. The mutational events underlying chronic lymphocytic leukaemias are less well understood but they also result in the steady expansion of a clone of cells, in this case functionally useless; eventually there is impaired tissue function as the leukaemic clone replaces normal cells.

Different types of leukaemia differ in their aetiology and also in the nature of the mutational events and thus in the nature of the disturbance in maturation, proliferation or both shown by the leukaemic clone. They also differ in age of onset, clinical and haematological features and prognosis.

**Acute lymphoblastic leukaemia**

Acute lymphoblastic leukaemia (ALL) is particularly a disease of childhood. Lymphocytes can be B-cells or T-cells so it is not surprising that ALL can be B-lineage (about ¾ of cases) or T-lineage (about ¼ of cases). Nothing is known about the cause of T-lineage ALL. A little bit is known about the cause of B-lineage ALL. Uncommon causes are (i) irradiation or exposure to chemicals *in utero* and (ii) mutagenic drugs. A much more common postulated mechanism is delayed exposure to an unidentified common pathogen. The evidence for this is an association with smaller family size, earlier birth order, higher socio-economic status and higher incidence in ‘green-field’ new towns in comparison with overspill new towns.

More is understood about the molecular mechanisms than about the causes.   
The oncogenic event in the lymphoid stem cell that gives rise to the leukaemic clone can be (i) formation of a fusion gene (ii) juxtaposition to the promoter of a different gene (iii) dysregulation of a gene by juxtaposition to enhancers of T-cell receptor genes. The net result is that a clone of cells continues to proliferate but cells do not mature or die. The clone thus expands progressively, replacing normal cells.

The pathological effects of clonal expansion are:

(i) The direct effects of the proliferation of the leukaemic cells (lymphadenopathy, hepatomegaly, splenomegaly, thymic enlargement (T-lineage ALL), bone pain, renal enlargement, testicular enlargement, cranial nerve palsies (meningeal infiltration), hyperuricaemia

(ii) The indirect effect of leukaemic cell proliferation, which leads to replacement of normal bone marrow cells by leukaemic cells (causing anaemia, thrombocytopenia, neutropenia).

The clinical features are therefore fatigue, lethargy, pallor, bruising and petechiae, bone pain, abdominal enlargement, lymphadenopathy and fever as a result of infection. Chest radiographs may show gross thymic enlargement (T-lineage ALL). Abdominal imaging may show hepatosplenomegaly and sometimes gross renal enlargement.

Essential investigations include blood count and film, immunophenotyping (to confirm T or B lymphoid cells), bone marrow examination and cytogenetic analysis.

The principles of treatment are:   
(i) blood products (red cells, platelets) to correct the effects of bone marrow failure;

(ii) systemic chemotherapy to kill off the cells of the leukaemic clone and permit normal cells to regenerate;   
(iii) intrathecal chemotherapy to destroy small numbers of leukaemic cells in the cerebrospinal fluid;   
In poor prognosis cases, bone marrow (or other haemopoietic stem cell) transplantation may be needed.

About ¾ of children with ALL can now be cured. [b.bain@imperial.ac.uk](mailto:b.bain@imperial.ac.uk)

**References**

Greaves M, Cancer: the Evolutionary Legacy. Oxford University Press, Oxford, 2000

Bain BJ, Leukaemia Diagnosis, 3rd Edn., Blackwell Science, Oxford, 2002.

Chest radiograph showing thymic enlargement in T-lineage ALL. Why do you think this is a feature of T-lineage but not B-lineage ALL?

(Figure from Bain BJ, Interactive Hematology Imagebank, Blackwell Science, 1999. This is available to you on the Intranet)