

Ministry of Defence

Synopsis of Causation

Chronic Myeloid Leukaemia

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Chronic myeloid leukaemia (CML) is a disorder defined by an abnormally high number of peripheral white blood cells and the presence of a chromosomal translocation resulting in a BCR-ABL fusion protein.
- 1.2. Several leukaemias resemble CML but, with no BCR-ABL fusion protein, are referred to as atypical chronic myeloid leukaemias. However, such variants are rare and not considered here. Certain leukaemias, notably acute lymphoblastic leukaemia, may also express BCR-ABL, but do not behave like CML.
- 1.3. CML is caused by an abnormal clone of cells that has acquired a survival advantage, thereby suppressing normal haemopoiesis.

2. Clinical features

- 2.1. The incidence is about 2 per 100,000 per year in the UK and, unlike most malignancies, does not vary greatly in different regions of the world, although it appears to be slightly more common in Caucasians.
- 2.2. The median age of presentation is about 65 and it is slightly more common in males than females. The incidence increases with age, following an approximately second power relationship with age ($\text{incidence} = k \cdot \text{age}^2$).
- 2.3. Although the crude incidence is increasing this reflects the age specific incidence and an increasingly elderly population. The age specific incidence appears to be constant.
- 2.4. Most cases present as a result of a full blood count taken for non-specific tiredness or malaise, typically from anaemia. Some cases may be detected from blood counts taken for unrelated reasons.
- 2.5. More specific symptoms include those arising from splenomegaly (fullness after small meals, a dragging sensation in the left upper abdominal quadrant, the more severe pain of splenic infarction), haemorrhage (abnormal platelet function, bleeding from various sites including ecchymoses), hyperviscosity (tiredness, headache, disturbed vision, confusion, paraesthesia, priapism), or rarely gout.
- 2.6. The diagnosis of CML is suspected from a raised white count in the absence of any infection that may explain the abnormality. Examination of the peripheral blood film shows both mature and immature myeloid forms, especially myelocytes, with a basophilia and eosinophilia. Depending on how advanced the disease is, there may be anaemia and a raised platelet count. A bone marrow aspirate is usually performed to confirm hypercellularity and assess the stage of the disease (see below).
- 2.7. The diagnosis is confirmed by detecting the BCR-ABL gene. This may be by karyotyping and detecting a Philadelphia chromosome, t(9;22), and/or by amplifying the gene using PCR and detecting a fusion fragment on a gel. The disease may also be caused by rarer variant translocations and some of these may not be apparent on conventional karyotyping.

3. Aetiology

- 3.1. It is thought that the BCR-ABL translocation is the sole genetic event that causes CML.
- 3.2. Unlike most leukaemias, no genetic predisposition to the leukaemia has been identified.
- 3.3. Unlike most leukaemias, smoking does not appear to predispose to CML, although the prognosis is worse once CML has been diagnosed.¹
- 3.4. CML may be caused by exposure to ionising radiation. It is well documented that CML was caused by exposure to the nuclear explosion in Hiroshima at the end of World War Two. However, this observation was not repeated after the Nagasaki explosion, the fallout from which differed in several respects from the former bomb. It is clear, therefore, that the nature of radiation that causes the translocation is important. Unlike some more common leukaemias, other studies of personnel subjected to lower levels of irradiation have failed to demonstrate a significantly increased risk of CML. It is not known whether this is because only rare forms of irradiation cause CML or whether there is an increased rate, but the leukaemia is too rare to detect a significant increase.
- 3.5. Several cases of CML have been reported after exposure to chemotherapy, but it is still unclear if the rate is more than expected by chance.²

4. Prognosis

- 4.1. CML follows a triphasic course. Initially the disease usually presents in “chronic phase”, which is easy to control using several therapies. The disease then transforms stochastically into an accelerated phase which in the past occurred at a rate of about 15% per year, during which the condition is more difficult to control. Finally, blast crisis supervenes, resembling acute myeloid or lymphoblastic leukaemia, but with a very poor prognosis. The annual rate of progression seems to be much lower since the introduction of tyrosine kinase inhibitors (see below).

Treatment

- 4.2. Treatment may be either symptomatic or curative. Symptomatic treatment by control of chronic phase disease is usually easy with drugs such as hydroxycarbamide (formerly hydroxyurea), which are associated with relatively few side effects. However, such treatment does not suppress the malignant clone to allow normal haemopoiesis to recover and does not prolong life expectancy, which is about 3-4 years on such monotherapy.^{3,4}
- 4.3. Use of alpha-interferon injections led to a suppression of the malignant clone in some cases and an overall increase of life expectancy of about one year.^{5,6} This increase may possibly be slightly lengthened by combining interferon with drugs such as cytarabine. However, interferon is associated with a significant number of side effects and is not now much used.
- 4.4. The only treatment shown to be curative is allogeneic bone marrow transplantation. This topic is too complex to be discussed in great detail in this synopsis. Patients can only receive transplants if they are relatively young and have suitable stem cell donors. Of those CML patients who receive conventional stem cell transplants, most can be cured, but about 20% of patients transplanted from related donors and 30% transplanted from unrelated donors die from complications of the treatment, mainly graft versus host disease. If the disease recurs after transplantation, cure can often be effected using donor lymphocyte infusions, though there is a risk of further graft versus host disease. Since the advent of imatinib treatment, transplants are now performed much less frequently than previously. However, they remain an important treatment option in selected patients, mainly treatment failures with imatinib (see below) or young patients at presentation.
- 4.5. Autologous bone marrow or peripheral blood stem cell transplantation may prolong life expectancy over hydroxycarbamide monotherapy, but this has not been proven. It is a little used therapy today.
- 4.6. The most widely used therapy today is the drug imatinib mesylate (Glivec), a specific inhibitor of the BCR-ABL tyrosine kinase activity. Although it has not been formally shown to improve life expectancy, as the trial set up to demonstrate this collapsed due to the patients randomised to non-imatinib arms requesting transfer to the imatinib arm, comparisons with historical controls have indicated a further survival advantage with the 4 year survival increasing from 40 to 50%.^{7,8} For previously untreated patients who receive imatinib, the complete haematological response rate is about 95%. Of particular note, the complete cytogenetic response rate is about 80%, with some of these patients achieving profound CML clone suppression. This latter subset of patients has a

particularly good prognosis, possibly achieving an “operational cure”.^{7,8} The side effects of imatinib are relatively mild. Nevertheless, some patients do not respond well to the drug and acquired resistance to the drug is a significant problem. In these patients, some of the older treatments must be considered.

- 4.7. Newer treatments are becoming available, notably variants of imatinib that appear to be effective against most of the structural BCR-ABL variants that mediate imatinib resistance.

5. Summary

- 5.1. Chronic myeloid leukaemia is a malignant disease of haemopoietic stem cells that presents with a high myeloid cell count. Although high dose ionising radiation has been shown to predispose to CML, in the vast majority of cases no cause can be identified. The disease can usually be controlled for some years using medication. However, using newer drugs such as imatinib, life may be prolonged substantially in comparison with previous therapy, and the annual progression rate seems to be much reduced. The only certain cure for the condition is a bone marrow transplant from a normal donor.

6. Related Synopses

Leukaemia and Myelodysplastic Syndromes.

The Myeloproliferative Disorders.

7. Glossary

allogeneic bone marrow transplantation	A transplant procedure using bone marrow collected from a matched healthy donor, usually a relative.
autologous	Derived from the patient's own tissue.
bcr-abl	The gene sequences that combine to form the fusion protein associated with CML.
chromosome	Self-replicating genetic structures of cells that contain the cellular DNA.
clone	A population of cells derived from a single progenitor cell.
cytogenetic	Relating to the study of the structure of chromosomes. Cytogenetic tests are carried out on blood and bone marrow samples to study chromosomal abnormalities.
fusion protein	Protein formed by a hybrid gene made by combining 2 gene sequences.
graft versus host disease	A serious and common complication of bone marrow transplantation. There is a reaction of the donated lymphoid cells against the patients own tissues because the donor's immune cells recognise the host cells as foreign and attack them. It causes a wide range of clinical problems, particularly involving the liver and gastrointestinal tract and may be fatal in some cases. It can be controlled with immunosuppressant drugs.
haemopoiesis	The formation and development of blood cells.
hyperviscosity	Increased viscosity of the blood.
karyotyping	Characterisation of the chromosomal complement of an individual or a species, including number, form and size of the chromosomes.

myelocytes	Cells produced by and contained within the bone marrow that produce white blood cells.
paraesthesia	Abnormal sensation, such as tingling or pins and needles.
splenomegaly	Enlarged spleen.
translocation	Rearrangement of a chromosome where a segment is moved from one location to another either within the same chromosome or to another chromosome.

8. References

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