ABC of clinical haematology

Chronic myeloid leukaemia

John Goldman

Chronic myeloid leukaemia is a clonal malignant myeloproliferative disorder believed to originate in a single abnormal haemopoietic stem cell. The progeny of this abnormal stem cell proliferate over months or years such that, by the time the leukaemia is diagnosed, the number of leucocytes is greatly increased in the peripheral blood. Normal blood cell production is almost completely replaced by leukaemia cells, which, however, still function almost normally.

Chronic myeloid leukaemia has an annual incidence of 1 to 1.5 per 100 000 of the population in the United Kingdom (about 700 new cases each year), with no clear geographical variation.

Presentation may be at any age, but the peak incidence is at age 40-60 years, with a slight male predominance. This leukaemia is very rare in children.

Most cases of chronic myeloid leukaemia occur sporadically. The only known predisposing factor is irradiation, as shown by studies of Japanese survivors of the atomic bomb and in patients who received radiotherapy for ankylosing spondylitis.

The clinical course of chronic myeloid leukaemia can be divided into a "stable" or chronic phase and an advanced phase, the latter covering both accelerated and blastic phases. Most patients present with chronic phase disease, which lasts on average four to five years. In about two thirds of patients the chronic phase transforms gradually into an accelerated phase, characterised by a moderate increase in blast cells, increasing anaemia or thrombocytosis, or other features not compatible with chronic phase disease. After a variable number of months this accelerated phase progresses to frank acute blastic transformation. The remaining one third of patients move abruptly from chronic phase to an acute blastic phase (or blastic crisis) without an intervening phase of acceleration.

Pathogenesis

All leukaemia cells in patients with chronic myeloid leukaemia contain a specific cytogenetic marker, described originally in 1960 by workers in Philadelphia and known consequently as the Philadelphia or Ph chromosome.

The Ph chromosome is derived from a normal 22 chromosome that has lost part of its long arm as a result of a balanced reciprocal translocation of DNA involving one of the 22 and one of the 9 chromosomes. The translocation is usually referred to as t(9;22)(q34;q11). Thus the Ph chromosome (22q-) appears somewhat shorter than its normal counterpart and the 9q+ somewhat longer than the normal 9.

The Ph chromosome carries a specific fusion gene known as BCR-ABL, which results from juxtaposition of the ABL proto-oncogene (from chromosome 9) with part of the BCR gene on chromosome 22. This fusion gene is expressed as a specific messenger RNA (mRNA), which in turn generates a protein called p210. This protein perturbs stem cell function, resulting in the chronic phase of chronic myeloid leukaemia, although the exact underlying mechanism remains unclear.

Researchers are working to inactivate the BCR-ABL gene and thereby reverse the leukaemic phenotype in chronic myeloid leukaemia cells.

Clinical features in patients with chronic myeloid leukaemia at diagnosis

Common

- Fatigue
- Weight loss
- Sweating
- Anaemia
- Haemorrhage—for example, easy bruising, discrete ecchymoses
- Splenomegaly with or without hepatomegaly

Rare

- Splenic infarction
- Leucostasis
- Gout
- Retinal haemorrhages
- Priapism
- Fever

Survival from chronic myeloid leukaemia

- The average survival from diagnosis is five to six years, but the range is wide
- Occasionally patients die within one year of diagnosis
- About 3% of patients may live more than 15 years without radical therapy

Formation of the Philadelphia chromosome resulting in a BCR-ABL fusion gene that generates a fusion protein (p210) responsible for the chronic myeloid leukaemia phenotype.

Chronic phase disease

Presentation

The characteristic symptoms at presentation include fatigue, weight loss, sweating, anaemia, haemorrhage or purpura, and the sensation of a mass in the left upper abdominal quadrant (spleen). Often the disease is detected as a result of routine blood tests performed for unrelated reasons, and a fifth of patients are totally asymptomatic at the time of diagnosis.

The spleen may be greatly enlarged before onset of symptoms. Treatment that reduces leucocyte count to normal usually restores the spleen to normal size

Much rarer symptoms at presentation include non-specific fever, lymphadenopathy, visual disturbances due to leucostasis (a form of hyperviscosity caused by an extremely high white cell count) or retinal haemorrhages, splenic pain due to infarction, gout, and occasionally priapism.

The commonest physical sign at diagnosis is an enlarged spleen, which may vary from being just palpable at the left costal margin to filling the whole left side of the abdomen and extending towards the right iliac fossa. The liver may be enlarged, with a soft, rather ill defined lower edge. Spontaneous and excessive bruising in response to minor trauma is common.

Diagnosis

The diagnosis of chronic myeloid leukaemia in chronic phase can be made from study of the peripheral blood film, but the marrow is usually examined for confirmation.

Usual peripheral blood findings in chronic myeloid leukaemia at diagnosis

- Raised white blood cell count ($30-400 \times 10^9/l$). Differential shows:
 - Granulocytes at all stages of development
 - Increased numbers of basophils and eosinophils
 - Blast (primitive) cells (maximum 10%)—never present in the blood of normal people
- Haemoglobin concentration may be reduced; red cell morphology is usually unremarkable; nucleated (immature) red cells may be present
- Platelet count may be raised ($300-600 \times 10^9/l$)

Marrow examination shows increased cellularity. The distribution of immature leucocytes resembles that seen in the blood film. Red cell production is relatively reduced. Megakaryocytes, the cells giving rise to platelets, are plentiful but may be smaller than usual.

Cytogenetic study of marrow shows the presence of the Ph chromosome in all dividing cells.

The patient's blood concentrations of urea and electrolytes are usually normal at diagnosis, whereas the lactate dehydrogenase is usually raised. Serum urate concentration may be raised.

Management

After diagnosis the first priority is a frank discussion with the patient. It is now customary to use the term leukaemia in this discussion and to explain to the patient that he or she may expect to live for several years with a near normal lifestyle. The clinician should explain the propensity of the disease to progress to an advanced phase. The choice of treatment with interferon alfa or hydroxyurea should be discussed.

If chronic myeloid leukaemia is diagnosed in pregnancy the woman should have the chance to continue to term. It seems that chronic myeloid leukaemia has no adverse effect on

Patient with massive splenomegaly in chronic phase chronic myeloid leukaemia.

Investigations to confirm suspected chronic myeloid leukaemia

Routine

- Full blood count including blood film
- Neutrophil alkaline phosphatase
- Urea, electrolytes
- Serum lactate dehydrogenase
- Bone marrow aspirate (degree of cellularity, chromosome analysis)

Optional

- Bone marrow trephine biopsy (extent of fibrosis)
- BCR-ABL chimeric gene by fluorescence in situ hybridisation or by polymerase chain reaction
- Vitamin B₁₂ and B₁₂ binding capacity
- HLA typing for patient and family members

Peripheral blood film from patient with chronic myeloid leukaemia showing many mature granulocytes, including two basophils (arrow); a blast cell is prominent (double arrow).

pregnancy and pregnancy has no adverse effect on the leukaemia.

The clinician may wish to mention at this stage the two ongoing Medical Research Council trials on chronic myeloid leukaemia. Patient information booklets produced by BACUP (British Association of Cancer United Patients) and by the Leukaemia Research Fund are extremely valuable as many patients will not retain all that is said at this first interview.

Interferon alfa—Interferon alfa is a member of a family of naturally occurring glycoproteins with antiviral and antiproliferative actions and is probably the drug of choice for managing chronic myeloid leukaemia in the chronic phase. Interferon alfa restores spleen size and blood counts to normal in 70-80% of patients. Of great interest is that 10-20% of patients achieve a major reduction or complete disappearance of cells with the Ph chromosome from their bone marrow (disappearance indicates complete remission). Interferon alfa initially causes flu-like symptoms, but these usually subside. Other more persistent side effects include anorexia, weight loss, depression, alopecia, rashes, neuropathies, autoimmune disorders, and thrombocytopenia. Toxicity leads to discontinuation in about a fifth of patients.

Allogeneic bone marrow transplantation—Patients under the age of 60 years who have siblings with identical HLA typing may be offered treatment by high dose cytoreduction (chemotherapy and radiotherapy) followed by transplantation of donor bone marrow. With typical family size in western Europe, about 30% of patients will have matched sibling donors. An appreciable mortality is associated with this approach, and in general, older patients (aged 40-60) fare less well than younger patients. Nevertheless the projected cure rate after allogeneic bone marrow transplantation is about 60%.

Autologous stem cell transplantation—For patients up to the age of 65 years for whom an allograft is excluded, autografting may be considered. For this purpose haemopoietic stem cells are collected from the patient's blood or marrow and cryopreserved. The patient then receives high dose cytoreductive chemotherapy, followed by reinfusion of the thawed stem cells. The morbidity and mortality associated with autografting are much lower than those associated with allografting, but autografting has no potential to cure. It probably prolongs life by one or two years in some cases.

Younger men should be offered cryopreservation of semen if necessary

Treatment with hydroxyurea

- Hydroxyurea inhibits the enzyme ribonucleotide reductase and acts specifically on cells of the myeloid series—that is, neutrophils, eosinophils, basophils, etc
- It is useful for rapid reduction of the leucocyte count in newly diagnosed patients
- Many haematologists start treatment with hydroxyurea then switch to interferon alfa once the patient's symptoms are relieved and the leucocyte count is restored to normal
- Hydroxyurea is also valuable for controlling chronic phase disease in patients who cannot tolerate interferon alfa
- It is usually started at 2.0 g daily by mouth; the usual maintenance dose is 1.0-1.5 g daily, titrated against the leucocyte count
- Treatment with hydroxyurea does not eradicate cells with the Ph chromosome
- Side effects are rare but include rashes, mouth ulceration, and gastrointestinal symptoms. The drug causes macrocytosis and megaloblastoid changes in the marrow

Treatment with busulphan

- Busulphan is an alkylating agent
- It is now reserved for chronic myeloid leukaemia resistant to hydroxyurea or in patients with poor compliance
- Prolonged or excessive dosage may lead to skin pigmentation, pulmonary fibrosis, and marrow aplasia

Eligibility and results of allogeneic transplantation for 100 newly diagnosed patients.

Advanced phase disease

Presentation

Advanced phase disease may be diagnosed incidentally as a result of a blood test at a routine clinic visit. Alternatively the patient may have excessive sweating, persistent fever, or otherwise unexplained symptoms of anaemia, splenic enlargement or splenic infarction, haemorrhage, or bone pain. In most cases the blast crisis is myeloid (that is, resembling acute myeloid leukaemia), and in a fifth of cases lymphoid blast crisis occurs.

Occasionally patients progress to a myelofibrotic phase of the disease, in which intense marrow fibrosis predominates, blast cells proliferate less aggressively, and the clinical picture is characterised by splenomegaly and pancytopenia consequent on marrow failure.

Management

Patients in advanced phase may benefit from introduction of hydroxyurea or busulphan if they have not previously received these. Splenectomy may be useful to improve thrombocytopenia or symptoms due to splenomegaly. Patients in a blastic phase may be treated by combination chemotherapy, though the possibility of treating localised pain or resistant splenomegaly by radiotherapy should not be forgotten. For those with myeloid transformations drugs suitable for treating acute myeloid leukaemia will control the leukaemic proliferation for a time. About 30% of patients will achieve a second chronic phase compatible with a normal lifestyle for months or years. Patients with lymphoid transformations should be treated with drugs appropriate to adult acute lymphoblastic leukaemia. Second chronic phase may be achieved in 40-60% of cases, more commonly in those who had a short interval from diagnosis to transformation. Patients restored to second chronic phase should receive craniospinal prophylaxis comprising five or six intrathecal injections of methotrexate. Cranial or craniospinal irradiation is probably not indicated.

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Criteria for advanced phase disease

- Increasing splenomegaly despite full doses of cytotoxic drugs
- Rapid white blood cell doubling time
- White blood cells poorly responsive to full doses of cytotoxic drugs
- Anaemia or thrombocytopenia unresponsive to cytotoxic drugs
- Persistent thrombocytosis ($> 1000 \times 10^9/l$)
- ☆ 10% Blasts in peripheral blood or marrow
- ☆ 20% Blasts plus promyelocytes in blood or marrow
- Acquisition of "non-random" chromosomal changes in addition to presence of Philadelphia chromosome
- Development of myelofibrosis

At times the chronic phase can be difficult to distinguish from advanced phase and can be diagnosed with confidence only in retrospect

Phases of chronic myeloid leukaemia showing progression to advanced phase.

The ABC of clinical haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

A father's death

The telephone call came late at night. "He's had a fall. They think he's had a skull fracture. He's unconscious—perhaps just concussion, but they're arranging a brain scan. He just faintly moved his thumb when I asked him to," said my mother, outwardly as cheerful as ever. My voice croaked back: "I understand; I'll come as soon as possible." Inwardly I cursed myself for not saying all the things I had wanted to say to him. I thought that he had a few more years.

It was the end of August, and nearly the end of the languorous summer holidays in the cottage in the upper reaches of the Loire. I lay awake, mentally preparing myself for the winding mountain roads across the Massif Central leading to Lourdes where I would join my mother and little handicapped niece on their annual pilgrimage. And of course my father.

Late next evening, exhausted after driving across France, I had to see him straight away. I knew that it was not logical as the facts would be clearer with the light of day. And then suddenly there he was in a cell-like room attached to countless drips and artificially ventilated.

He was recognisable, but only just. I felt his bristly cheek against mine as I would do with our customary farewell pecks. I caressed his arm and shoulder and chest—so warm and life-like, despite the dehumanising surroundings. I visited the room three times. Each visit was accompanied by searing emotion and an irresistible urge to touch him that took me quite by surprise. Quickly, the facts emerged from

the fog. No skull fracture, no evacuable clot. A stroke, and unconscious, though—a thin ray of hope—still sedated.

Most of the time was spent outside the hospital. I thought that it was important to piece together my father's last few hours. How he had struggled up the hill to confession the day before; and how he had managed to spend some time with his little granddaughter who suffered from the same disabling spasticity as he, since his hemiplegia 15 years before. How after mass the next day he was seen at lunch commanding the attention and laughter of several young women whom he had managed to sit with. How he had rested in his room as usual, but had vomited and telephoned to ask the hotel staff to help clear it up. But what had happened during the next few hours before he was found collapsed on the bathroom floor? His room mate reasoned that there was no evidence of panic. His lapse into unconsciousness must have come quite quickly.

Suddenly, after three days in a coma, he was dead. Great relief. But gone too was the hope against hope of ever seeing that mischievous twinkle in his eye again.

Now, as I sit at my father's desk, I stumble across a photograph of him. The pangs of sadness come, but are so much less now. How important were those experiences during his final brief illness at Lourdes.

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