Chronic myeloid leukaemia

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Abstract

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22. This is termed the Philadelphia chromosome, and leads to production of the fusion onco-protein BCR-ABL, a 210 kDa constitutively active tyrosine kinase. CML has three distinct phases: the chronic, accelerated and blast phases. Most patients (85%) present in the chronic phase, which is associated with leucocytosis and splenomegaly. More advanced phases are associated with bone marrow failure and carry a poor prognosis. The introduction of tyrosine kinase inhibitors (TKIs; imatinib, dasatinib, nilotinib, bosutinib, ponatinib) has altered the clinical course of CML for most patients, turning it from a fatal leukaemia to a chronic disorder managed with oral medication. Patients with chronic-phase CML have excellent levels of response to TKIs, and individuals with an optimal response can expect a normal lifespan. However, resistance to TKIs is seen, particularly in the advanced phases of CML. In these patients, allogeneic stem cell transplantation may warrant consideration. With increasing experience in the use of TKIs, different adverse effect profiles are emerging and require consideration when choosing the most suitable TKI for an individual patient.

Keywords Allogeneic stem cell transplantation; BCR-ABL; chronic myeloid leukaemia; dasatinib; imatinib; nilotinib; Philadelphia chromosome; ponatinib; quantitative RT-PCR; tyrosine kinase inhibitors

Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm characterized by an excess of granulocytes (neutrophils, basophils, eosinophils). It is a clonal disorder that originates from a bone marrow haemopoietic stem cell. The characteristic and diagnostic genetic abnormality in CML is the Philadelphia chromosome.

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Key points

- Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder associated with the Philadelphia chromosome and its onco-protein product, BCR-ABL
- CML has three progressively more aggressive phases: chronic, accelerated and blast phases
- Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML and are the gold standard therapy for chronic-phase CML
- Co-morbidities should be considered when choosing the most appropriate TKI for a patient
- Allogeneic stem cell transplantation should be considered for patients failing two or more TKIs or who have advanced-phase CML
- Selected patients have successfully stopped TKIs in clinical trials

Epidemiology

CML has a worldwide annual incidence of 1–1.5 cases per 100,000 population. It can occur at any age, but half of cases are diagnosed in people >65 years of age. There is a slight male predominance and a higher incidence among those with radiation exposure.

Pathology and pathogenesis

The presence of the Philadelphia chromosome results in the fusion oncogene *BCR-ABL* owing to the juxtaposition of the 3′ portion of the Abelson (*ABL*) gene from the long arm of chromosome 9 with the 5′ portion of the breakpoint cluster region (*BCR*) on the long arm of chromosome 22 (Figure 1, left panel). The resulting constitutively active tyrosine kinase, BCR-ABL, is a 210 kDa protein essential for the unregulated proliferation of myeloid cells characteristic of CML. With disease progression, additional cytogenetic abnormalities can develop, as well as mutations of the BCR-ABL kinase domain, which are associated with treatment resistance.

Disease course

CML is divided into three phases: the chronic, accelerated and blast phases (Table 1). Approximately 85% of CML patients are diagnosed in the chronic phase, and 15% in the more aggressive accelerated or blast phases. Blast-phase CML can be lymphoid or myeloid and behaves as a poor-prognosis acute leukaemia with frequent and rapid development of fatal treatment resistance.

Historically, CML had a median survival of 5–7 years. However, the introduction of BCR-ABL tyrosine kinase inhibitors (TKIs; e.g. imatinib) has revolutionized its treatment. The 5-year overall survival in the chronic phase is 92–95%,[2] and life expectancy approaches that of the general population (see Bower et al. in Further Reading). The outcome in blast-phase CML

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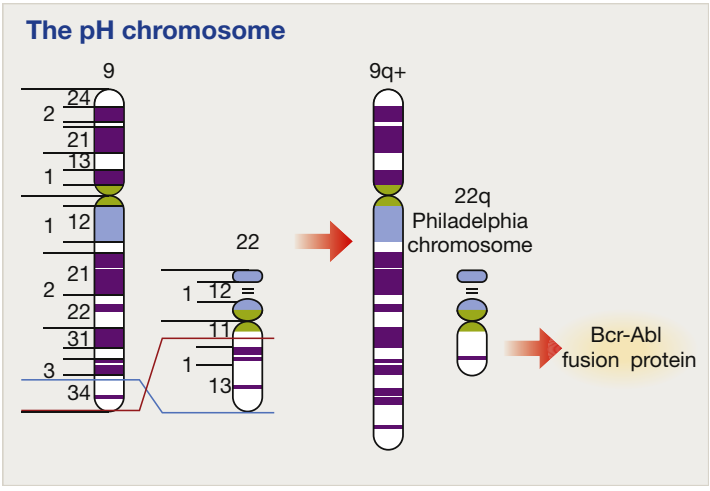

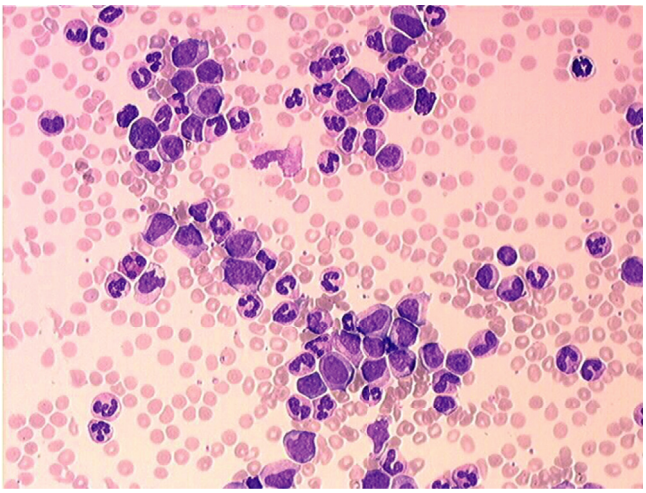

Figure 1 Characteristic features of CML. Left: the Philadelphia (Ph) chromosome; right: blood film from a patient with chronic-phase CML, demonstrating neutrophilia, basophilia and left shift with frequent myelocytes and metamyelocytes.

remains very poor, with a median survival of 7–11 months despite multiple aggressive therapies.

Diagnosis

Approximately 30% of patients with CML are asymptomatic, the diagnosis being made following an incidental finding of leucocytosis on a full blood count. Symptoms at presentation are often non-specific and include fatigue, night sweats, weight loss, abdominal discomfort as a result of splenomegaly (present in 50–90% patients at diagnosis) or splenic infarction, spontaneous bleeding or bruising. Patients presenting with very high white cell counts (>100 $\times$ 10^9/litre) can have symptoms associated with leucostasis, including headaches, visual disturbance, dyspnoea and priapism.

Criteria required for the diagnosis of chronic, accelerated and blast-phase CML according to the World Health Organization (WHO) classification[1]

Phase	WHO diagnostic criteria
Chronic phase	Absence of all features listed below
Accelerated phase	One or more of the following features: • Blasts comprise 10–19% of peripheral blood white cells or nucleated bone marrow cells • Peripheral blood basophilia of ≥20% of peripheral blood white cells or nucleated bone marrow cells • Persistent thrombocytopaenia (<100 $\times$ 10^9/litre) unrelated to therapy, or persistent thrombocytosis (>1000 $\times$ 10^9/litre) unresponsive to therapy • Increasing spleen size and white cell count unresponsive to therapy • Cytogenetic clonal evolution
Blast phase	One or more of the following features: • Blasts ≥20% of peripheral blood white cells or nucleated bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in a bone marrow biopsy

Table 1

Investigations

In CML, the white cell count at diagnosis can range from 15 $\times$ 10^9/litre to >200 $\times$ 10^9/litre. Very high white cell counts are often associated with symptoms; thrombocytosis can also be a feature. The blood film shows characteristic features, with expansion of all types of myeloid cells including neutrophils, basophils, eosinophils and their precursors (Figure 1, right panel). Nucleated red cells are often seen. A bone marrow aspirate taken during the chronic phase demonstrates a hypercellular marrow with myeloid hyperplasia and an increased myeloid:erythroid ratio. The percentage of blasts in the peripheral blood and bone marrow is crucial for staging CML (Table 1). A bone marrow trephine sample shows a packed marrow, and fibrosis can be a feature.

Fluorescence *in situ* hybridization or cytogenetics on a bone marrow specimen reveals the Philadelphia chromosome. The *BCR-ABL* fusion gene is demonstrated by qualitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells.

Differential diagnosis

- Acute myeloid leukaemia
- Acute lymphoblastic leukaemia
- Chronic neutrophilic leukaemia
- Myelofibrosis
- Granulocyte-colony stimulating factor (GCSF) therapy
- Severe sepsis
- Chronic eosinophilic leukaemia
- Essential thrombocytosis
- Bone marrow infiltration with non-haematological malignancy.

Management

Patients presenting with a very high white cell count may require the cytoreductive agent hydroxycarbamide and leucapheresis to rapidly reduce the white cell count until the diagnosis has been confirmed.

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