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Treatment strategies for CML

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Little important progress was made in terms of prolongation of life for patients with chronic myeloid leukaemia (CML) until the advent of interferon-alpha and allogeneic stem cell transplantation in the 1980s. However, in 1998 the introduction of imatinib, the first tyrosine kinase inhibitor (TKI) that specifically targets the BCR-ABL1 oncoprotein, has fundamentally altered treatment strategies for patients in all phases of CML. Imatinib is now recommended as initial treatment for all patients who present in chronic phase (CP) and about two-thirds of patients so treated will be in continuing complete cytogenetic response 7 or more years after starting therapy. A small proportion of these patients can stop the drug without molecular evidence of relapse. For the minority of patients who are judged to have failed initial treatment with imatinib at standard dosage or increased dosage, the use of second-generation TKI or allogeneic stem cell transplantation must be considered.

Leukaemia was first recognised as an entity arising *de novo* without identifiable external cause in the 1840s, first by Velpeau in Paris and soon after by Virchow in Berlin and by Hughes Bennett in Edinburgh [1]. Treatment throughout the 19th century was largely ineffective, although there was clear evidence that arsenic administered in different inorganic forms could reduce the leucocyte count and probably also shrink the enlarged spleen. However, it did not demonstrably prolong life. The introduction of radiation therapy at the beginning of the 20th century was a simpler and less toxic method of controlling symptoms, but it too did little, if anything, to prolong life. An important advance was the introduction of the modified alkylating agent busulfan in 1953; this agent could be given orally on an outpatient basis and it restored the haematological picture to normal with great reliability. It proved to be superior to radiation therapy in one of the earliest randomised clinical

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trials in leukaemia [2] but inadvertent overdosage could cause irreversible marrow aplasia, and many in the 1970s preferred to use hydroxyurea, which was easier to handle in the clinic. Both agents were highly effective in controlling the symptoms of CML but neither delayed the onset of advanced phase disease.

The demonstration in 1979 that patients with CML in chronic phase (CP) could be treated by high-dose chemoradiotherapy followed by transfusion of marrow cells from their genetically identical twins, after which marrow haematopoiesis remained Ph-negative without further treatment, was an important landmark in the management of CML [3]. This observation led investigators on both sides of the Atlantic to test the role of allogeneic bone marrow transplant for younger CML patients who were still in the chronic phase and had genetically HLA-identical siblings [4,5]. It rapidly became clear that such transplants, despite the real hazards of post-transplant infections and graft-versus-host disease, could induce long-term Ph-negativity and thereby delay or prevent entirely the onset of transformation. Thus, allogeneic stem cell transplantation became the treatment of choice for eligible patients.

In the early 1980s, investigators in Houston demonstrated first that administration of interferon-alpha could induce Ph-negativity in a minority of patients with CML in CP and, subsequently, they showed that such responders lived longer than the majority of patients who obtained no cytogenetic responses [6]. A careful prospective comparison of survival in patients treated with hydroxyurea and those treated with interferon-alpha performed in Italy demonstrated a real, although modest, prolongation of life with interferon-alpha treatment [7]. Subsequently, a French multicentre study showed convincingly that, at least in the short-term, the use of interferon-alpha, combined with cytarabine, induced better cytogenetic responses and superior survival than the use of interferon-alpha alone [8]. Thus, until the end of the 1990s, the recommended treatment for patients presenting with newly diagnosed CML in CP was allogeneic stem cell transplant (allo-SCT) if they were relatively young and had a suitable donor; for others, interferon-alpha with or without cytarabine was an acceptable alternative. It was interesting to note that a small proportion of patients who had been treated with interferon-alpha for some years and had achieved durable Ph-negativity could stop taking the drug without evidence of subsequent relapse [9]. Thereafter, the management of CML changed fundamentally with the introduction in 1998 of imatinib mesylate, now more usually referred to as imatinib.

Imatinib

Imatinib is a 2-phenylaminopyrimidine derivative developed originally as a general tyrosine kinase inhibitor (TKI) that was modified chemically so as to compete with ATP for the ATP-binding site or P-loop in the Abl protein and thereby block the dysregulated enzymatic function of the Bcr-Abl oncoprotein. It was first used in 1998 to treat patients judged to be resistant to interferon-alpha and early results showed that it was able to re-establish Ph-negative (presumably normal) haematopoiesis in a proportion of these patients. The maximum tolerated dose was not formally established [10]. This led rapidly to the design and implementation of a multinational prospective clinical study,

Table 1
Unanswered questions in the initial or early management of CML.

1. How important is it to aim for a major molecular response is a person who has achieved a CCyR?
2. Are imatinib plasma levels useful for adjusting imatinib dosage in the clinic?
3. How should we assess the issue of compliance/adherence in a person who has been taking imatinib for say two years?
4. Should some patients who fail imatinib at 400 mg/daily be offered to 600 mg or 800 mg/daily or should all go directly to a second generation TKI?
5. To what extent should the finding of KD domain mutations (other than T315I) dictate choice of subsequent therapy?
6. At what stage is a patient clearly a candidate for allo-SCT?
7. When can imatinib safely be stopped in a responding patient (if at all)?
8. What is the best way of managing a woman who wants to have a child?
9. Should any patient receive second generation TKIs as primary treatment for CML-CP outside the context of a clinical trial?