Revised advice on use of imatinib for chronic myeloid leukaemia

AUTHOR Ken Campbell, FIBMS, CertHMS, is clinical information officer, Leukaemia Research Fund. (This article was written in a personal capacity.)


NICE guidance that imatinib be available to all patients newly diagnosed with chronic myeloid leukaemia has been welcomed by clinicians and patient groups. The drug is expected to transform the management of CML.

Chronic myeloid leukaemia (CML) is a chronic, clonal, myeloproliferative disorder that is typically triphasic. There is a prolonged chronic phase (three to six years), followed in most cases by an accelerated phase (three to 12 months) after which there is disease progression, and finally an aggressive, almost always terminal, blast phase (sometimes called blast crisis). Progression from chronic phase to accelerated or blast phase is termed transformation. Patients may present in accelerated phase or in blast phase, but this is rare. The affected cell is an early haemopoietic stem cell; evidence for this includes the fact that the blast phase may be lymphoid, myeloid or mixed, which indicates that the affected cell in CML has not committed to lymphoid or myeloid differentiation (Savage and Antman, 2002).

Treatment guidelines

The National Institute for Clinical Excellence (NICE) was set up in April 1999 with four stated aims:

● To speed up NHS use of interventions that are both clinically and cost-effective;

● To encourage more equitable access to health care (that is, reduce the so-called postcode lottery of care);

● To provide better and more rational use of available resources by focusing the provision of health care on the most cost-effective interventions;

● To encourage the creation of innovative technologies.

In a detailed review about the role of NICE in cancer medicine, Littlejohns et al (2003) wrote: ‘Although NICE’s appraisal guidance remains advisory at the professional/patient interface, the funding to enable its implementation must be made available at an institutional level.’ This means that if a clinician prescribes within NICE guidelines, regardless of the cost of a drug, the health authority must provide the funding.

The NICE recommendations

Interim NICE guidance issued last year confined access to imatinib to patients who were either intolerant of interferon-alpha or whose disease was unresponsive to IFNα.

The conservative recommendation was largely based on the absence of definitive studies demonstrating extension of survival or of progression-free survival.

It was pointed out in the responses to this interim recommendation that the indolent natural history of CML meant that such evidence would take many years to collect and meanwhile patients were being deprived of the unequivocal quality-of-life benefits that imatinib therapy could offer (Hahn et al, 2003; Leach et al, 2002).

It was expressly stated that imatinib treatment started in the chronic phase should not be continued routinely following transformation to accelerated or blast phase. Imatinib should be used in this case only in the context of a clinical study, with systematic data collection and national aggregation of data to determine the outcomes of such treatment. The guidance gave no explicit advice on the management of a patient whose disease is either resistant de novo or becomes resistant to imatinib; that secondary resistance develops is well established.

There was concern that cash-strapped health authorities may seek to restrict use of imatinib in these circumstances – in the absence of specific NICE guidance they are entitled so to do.

A recent paper in Cancer (Cortes et al, 2003) reported the surprising finding that age should no longer be seen as a significant prognostic factor for patients treated with imatinib. It had been suspected that the consistently poor prognosis for older patients was the result of an intrinsically worse disease biology, but the new evidence suggests that the poor outcomes were primarily linked to treatment-related factors.

The revised NICE guidance (2003) includes a wider patient population. Imatinib should be used:

● As first-line treatment for patients with Philadelphia-chromosome-positive (Ph+ve) CML in the chronic phase;

● As an option for patients with Ph+ve CML who initially present in the accelerated phase or with blast crisis;

● As an option for people who present in the chronic phase, and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.

For patients receiving IFNα as first-line treatment, NICE recommends that the decision on whether to switch to imatinib should be based on a discussion between the patient and their clinician.

Stem-cell transplant

It remains accepted that the only potential curative treatment for CML is an allogeneic (donor) stem-cell transplant. But most patients are either too old or too unfit to undergo the procedure, or there is no suitable donor. For these patients, the treatment of choice is clearly imatinib.
For the minority of those who are eligible for a transplant and who have a donor, the decision is more difficult. There is, as yet, insufficient evidence to determine whether imatinib has the potential to achieve cure or, alternatively, whether patients, while not cured, can achieve a normal or near-normal lifespan on active treatment with the drug.

A key question is whether imatinib can delay the normally inexorable rate of transformation, but given the indolent nature of CML, it will take 10–15 years to establish this. Against the accepted curative potential of allelic geneic stem-cell transplant must be set the significant treatment-related morbidity and mortality of the procedure. Experience indicates that the best results from stem-cell transplant are obtained when the procedure is carried out within a year of diagnosis, with the patient still in the chronic phase.

Many experts believe that, given the high rate of metabolic clearance rate achieved with imatinib, this one-year watershed may no longer apply. There is currently a roughly even split between experts who recommend immediate transplantation for any younger patient with a matched sibling donor and experts who would advise a trial of imatinib, reserving stem-cell transplant for those who do not respond or whose disease progresses on therapy.

**Resistance**

A further dilemma is how to manage patients whose disease is either de novo resistant or who develop resistance to imatinib while on therapy. There is evidence from both clinical and laboratory studies of the various mechanisms through which CML cells may acquire resistance to imatinib (Hochhaus et al, 2002). A detailed discussion of clinical decision-making for CML in the imatinib era has been published by John Goldman and colleagues (2003) at Hammersmith Hospital – and is accompanied by a series of commentaries by recognised experts. Where CML does not initially respond to imatinib the recommendations are to:

- Persist at the current dosage – patients may show a delayed response;
- Increase the dosage;
- Combine imatinib with another drug or drugs;
- Offer a donor transplant – the preferred option if a good donor is available for a fit patient;
- Offer a non-myeloablative stem-cell transplant or a transplant using a less-than-ideal donor.

In the case of secondary resistance, the first of these is obviously not an option, but the others may be applicable. However, NICE does not make recommendations on the management of de novo or secondary imatinib resistance. An additional option suggested by one of the commentators on the Hammersmith policy is to employ pulsed therapy for responding patients, in an attempt to reduce the selection pressure leading to the emergence of resistant clones.

**Conclusion**

NICE guidance that imatinib should be available to all patients who have been newly diagnosed with chronic myeloid leukaemia is a welcome development.

It can be expected to transform management of CML, although NICE has not, as yet, addressed issues such as the management of de novo or secondary imatinib resistance. There is a need for clinical trials to resolve these questions – the greatest obstacle to mounting such trials may well be the public perception of imatinib as a ‘wonder drug’ and a consequent reluctance to participate in trials investigating alternative treatments.

**BOX 1. THE PHILADELPHIA CHROMOSOME AND THE BCR-ABL ONCOGENE**

Chronic myeloid leukaemia (CML) is characterised by the presence of the Philadelphia chromosome. This is an abnormal small chromosome, resulting from a translocation between chromosomes 9 and 22 and bearing a fusion gene called BCR-ABL*. BCR-ABL forms when ABL on chromosome 9 is brought next to BCR on chromosome 22.

ABL encodes for a tyrosine kinase, an element in the signalling pathway between cell surface receptors and the nucleus, a process called signal transduction. This gene is normally ‘off’ and switches ‘on’ in response to an upstream messenger. The BCR-ABL fusion gene is permanently on. The ABL protein drives cell proliferation and survival via multiple pathways.

BCR-ABL activates its substrates by phosphorylation, transferring a phosphate group from ATP* on to the target protein. Imatinib acts by blocking the site on BCR-ABL where the ATP molecule must bind for phosphorylation to occur. In so doing, it blocks the multiple downstream pathways that lead to malignant transformation of the CML cell.

The ‘gold standard’ for CML therapy is a major cytogenetic response (MCR). A lesser response to treatment is a complete haematological response, in which routine haematological testing cannot detect CML cells but the BCR-ABL fusion gene is detectable. Imatinib achieves this in a high proportion of cases; older therapies achieved a much lower rate of MCR and caused more severe side-effects.

The presence, albeit at low levels and transiently, of BCR-ABL gene expression in the white cells of a healthy person is evidence to support the stem cell nature of CML. The translocation has presumably occurred in a relatively mature myeloid progenitor – such cells are incapable of assuming the CML phenotype. Only when a BCR-ABL fusion gene is present in a haematological stem cell can a CML clone emerge.

*ABL – Abelson oncogene; ATP – adenosine triphosphate; BCR – breakpoint cluster region gene

**REFERENCES**


*This article has been double-blind peer-reviewed.*

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