Improving the management of chronic myeloid leukaemia

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Until recently the therapeutic options available to patients diagnosed with chronic myeloid leukaemia hinged on their suitability for allogeneic bone marrow transplantation. With the advent of new agents targeting the specific molecular pathways involved in the disease, drug therapies may have an increasingly important role in improving outcome.

Prospects are improving for the effective treatment of chronic myeloid leukaemia (CML). A new signal transduction inhibitor Glivec (STI571, imatinib mesylate, Novartis Pharmaceuticals, Basel) that specifically targets the molecular abnormality underlying the condition is showing encouraging results.

CML is a rare disease, with an annual incidence of 1–1.5 per 100 000 of the population in the UK and about 700 new cases each year, as extrapolated from regional data. The disease can present at any age, but the peak incidence occurs at 40–60 years of age, with a slight predominance in men (Thomas et al, 2001). Most cases occur sporadically. The only known predisposing factor is exposure to radiation, as seen in patients treated with radiotherapy for ankylosing spondylitis. The median survival is currently only 4–6 years from the time of diagnosis (Chronic Myeloid Leukemia Trialists' Collaborative Group, 2000).

PATHOGENESIS

The pathogenesis of CML at the molecular level is now well understood (Witte, 2001). All leukaemic cells in patients with CML contain a specific cytogenetic marker, originally identified in 1960 by researchers in Philadelphia, so known as the Philadelphia (Ph) chromosome. This is derived from chromosome 22, which has lost part of its long arm as a result of a reciprocal translocation between chromosome 22 and chromosome 9. The Ph chromosome carries a specific fusion gene — BCR-ABL — which results from the 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, which in turn generates a protein called p210. This protein disrupts stem cell function, resulting in the chronic phase of CML, although the precise underlying mechanisms remain unclear (Sawyers, 1999).

The characteristic clinical features of CML include fatigue, weight loss, sweating, anaemia, haemorrhage and the sensation of a mass in the upper left abdominal quadrant as a result of splenomegaly (*Table 1*). The disease is often detected as a result of routine blood tests, with one-fifth of patients being totally asymptomatic at the time of diagnosis. The condition is diagnosed by the finding of raised white blood cell count (30–400x10^9/litre, normal range 4–11x10^9/litre)

TABLE 1.
Common clinical features at diagnosis in patients with chronic myeloid leukaemia

Anaemia
Haemorrhage — including easy bruising
Splenomegaly, with or without hepatomegaly
Fatigue
Sweating
Weight loss
Occasionally splenic infarction, leucostasis, gout, retinal haemorrhages, priapism, fever

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in a peripheral blood film. Marrow examination shows increased cellularity. Cytogenetic study of marrow will reveal the presence of the Ph chromosome in dividing cells.

CURRENT TREATMENT OF CML

Drugs currently used in the treatment of CML include interferon-alpha, hydroxyurea, cytarabine and busulfan. Interferon is the standard therapy for most patients who are not candidates for a bone marrow transplant, normalizing blood counts (haematological response) and reversing the chromosomal abnormality (cytogenetic response) in a proportion of patients before the disease undergoes blastic transformation. It restores spleen size and blood counts to normal ranges in 70–80% of patients, and achieves reduction or complete disappearance of cells with the Ph chromosome from the bone marrow in 10–20% (Allan et al, 1995). A survival advantage has been demonstrated in a number of studies (Chronic Myeloid Leukemia Trialists' Collaborative Group, 2000). However, it is associated with a high rate of troublesome side-effects, including flu-like symptoms, anorexia, depression, neuropathy and autoimmune disorders. Toxicity results in drug discontinuation in about one-fifth of patients.

An allogeneic bone marrow transplant — using healthy stem cells from the bone marrow of a closely matched donor — currently offers the best hope for a cure. However, donors are not available for most patients with CML — suitable donors can be found for only about 30% of patients — and advanced age or other complicating medical factors make a transplant unsuitable for others. For patients up to the age of 55 years (and in some centres 45 years old) where an allograft is out of the question, autografting is sometimes considered. Haemopoietic stem cells are harvested from the patient's blood or marrow and cryopreserved. The patient is then given high-dose cytoreductive chemotherapy followed by reinfusion of the thawed stem cells. The morbidity and mortality associated with autografting are much lower than with allografts, but there is no potential for complete cure. Studies suggest it prolongs life by 1–2 years in some patients (McGlave et al, 1994).

TARGETING THE MOLECULAR ABNORMALITY UNDERLYING CML

STI571 offers a major step forward in the management of CML because of its highly targeted action. It acts as a signal transduction inhibitor that targets one particular protein — p210 BCR-ABL — which is produced as a result of the chromosomal abnormality occurring in patients with the condition. It is widely accepted that the BCR-ABL fusion gene usually found in association with the Ph chromosome is the proximate cause of chronic phase CML (McLaughlin et al, 1987). STI571 appears to occupy the tyrosine kinase pocket of the BCR-ABL protein, blocking access to ATP and preventing the cascade of reactions that eventually results in uncontrolled cell proliferation (Buchdunger et al, 1996).

Preliminary experience in patients with chronic phase CML shows that the drug rapidly restores the leucocyte count to normal, induces major cytogenetic responses in 49% of patients and eradicates the Ph-positive clone in 30% of patients (Druker et al, 2001a). STI571 is the first successful drug used in oncology that appears to work by inhibiting a specific signal transduction pathway (Druker et al, 1996).

Trials with STI571 have shown impressive response rates in all phases of CML. In studies of patients with chronic phase CML, 88% of patients showed a haematological response, while 49% showed a major cytogenetic response to STI571 (Druker et al, 2001a). Nearly two-thirds (63%) of patients with accelerated phase disease showed a haematological response to the drug, with major cytogenetic response in 21%. In myeloid blast crisis the new agent was still able to show improvement — with 26% haematological response and 13.5% major cytogenetic response (Druker et al, 2001b). Based on the clinical trial results, STI571 was licensed in the USA for the treatment of CML in May 2001 and a license application has been submitted for approval in Europe, which is expected to be granted in October 2001.

STI571 has proved to be generally well tolerated. The most common side-effects are fluid retention and weight gain with some patients experiencing mild nausea in early trials where the drug had to be taken on a empty stomach. Anecdotally, patients generally feel much better on STI571 than when they are treated with interferon (current trials are performing quality of life studies). A trial is now underway comparing the effects of STI571 with the current 'gold standard' treatment of interferon with cytarabine in newly diagnosed CML. Recruitment closed in January this year, with 1106 patients recruited in 7 months. The primary endpoint is survival, with cytogenetic response as the secondary outcome measure. Treatment will continue for up to 5 years. The PISCES study (http://www.pisces-project.org) is the first study to combine STI571 with interferon and there will shortly be a new international study comparing this combination to STI571 alone (SPIRIT).

CONCLUSION

The development of STI571 is set to change the management of CML over the next few years. More than 10 000 patients have now taken the drug, with encouraging clinical benefits and good tolerability. Ongoing trials will demonstrate the value of using STI571 in early disease, and compare it with current standard treatments. For now, it seems sensible to continue consideration of allografts for younger patients if a sibling donor is available. In older patients or where there is no donor, STI571 offers an important new option. HM

Conflict of interest: Dr S O'Brien has been supported in clinical trial work by Novartis Pharmaceuticals.

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KEY POINTS

- Chronic myeloid leukaemia is characterized by the detection of the Philadelphia chromosome which gives rise to the specific chimeric fusion gene BCR-ABL.
- The only known curative therapy for chronic myeloid leukaemia is allogeneic haemopoietic stem cell transplantation.
- STI571 acts as a signal transduction inhibitor targeting the tyrosine kinase function of p210 BCR-ABL.
- STI571 has been shown to achieve haematological and cytogenetic remissions in chronic phase, accelerated phase and blast crisis and is generally very well tolerated.
- STI571 offers an effective therapeutic option to patients not suitable for bone marrow transplantation.