An update on chronic myeloid leukaemia

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Chronic myeloid leukaemia (CML) is a clonal disorder of haematopoietic stem cells characterised by the Philadelphia (Ph) chromosome t(9;22)(q34;q11). Greater understanding of the molecular biology of CML has recently yielded remarkable advances in treatment and may revolutionise the management of this disease.

Clinical features

CML has a yearly incidence of 1–1.5 cases per 100,000 population[1]. There are approximately 3,000–4,000 patients in the UK. CML occurs at any age, with a median age of onset at 55–60 years and median survival of 4–5 years. One-third of the cases are asymptomatic at diagnosis[2], and the rest present with fatigue, weight loss and night sweats. Splenomegaly, sometimes massive, occurs in up to 50%.

CML is triphasic. Over 85% of patients present in chronic phase which lasts 2–7 years (median 4.2 years). The chronic phase transforms abruptly to blast crisis in 50% of cases. Transformation is least likely during the two years immediately after diagnosis, but later the annual progression rate becomes 20–25%[3]. In the other 50%, CML evolves less dramatically to accelerated phase then blast crisis, months or years later.

In the *chronic phase* there is granulocytosis, with left shift, basophilia and sometimes eosinophilia. Anaemia is common, and platelets are typically normal or elevated. A low neutrophil alkaline phosphatase score can help to differentiate the neutrophilia of CML from other causes. In the *accelerated phase*, organomegaly and cell counts become increasingly refractory to treatment. The disease progresses inevitably to *blast crisis* and then treatment becomes ineffective.

Prognostic features

Two prognostic scores based on risk factors can aid therapeutic decisions. A high risk, but potentially curative, therapy may be acceptable to a patient with poor risk disease, but a more conservative approach may be preferred by a patient with a better prognosis:

- The *Sokal score* uses patient age, peripheral blood blast percentage, platelet count and spleen size at diagnosis.
- The *Hasford score* adds peripheral blood basophil and eosinophil counts to those measurements.

These scores, which define high, intermediate and low risk groups, with median survivals of 45, 69 and 102 months respectively, are more applicable to the study of groups than of individuals and should be used cautiously.

Molecular biology

In CML the Ph chromosome is found in myeloid, erythroid, monocytoid and megakaryocytic lineages, and in B and occasionally T lymphoid lines. The translocation brings *ABL* gene sequences from chromosome 9 into juxtaposition with the *BCR* gene on chromosome 22, creating a BCR-ABL fusion gene. This encodes a 210 kD protein (p210B*CR-ABL*) with dysregulated tyrosine kinase activity[4].

Numerous substrates are phosphorylated by p210BCR-ABL, resulting in abnormal signal transduction in many cellular pathways. This causes dysregulated proliferation, reduced adhesion to the extracellular matrix and reduced response to apoptotic signals.

Treatment

Management of chronic phase disease

Therapeutic decision making in chronic phase CML is currently difficult. A balance must be struck between 'proven' high-risk procedures such as allogeneic stem cell transplantation (SCT) and 'unproven' promising therapies such as the tyrosine kinase inhibitor STI571.

Hydroxyurea and busulphan have been mainstays of therapy for many years. Although both induce haematological remission in up to 90% of patients, neither induces cytogenetic remission or reduces the rate of blast transformation. Patients treated with hydroxyurea have a longer median survival[5].

Key Points

Chronic myeloid leukaemia (CML) has a yearly incidence of 1–1.5 cases per 100,000 population.

CML occurs at any age, with a median age of onset at 55–60 years and a median survival of 4–5 years.

CML is triphasic – these being the chronic phase, the accelerated phase, and the inevitable blast crisis.

Remarkable, and perhaps revolutionary, advances in the treatment of CML have taken place recently, although these should still be considered 'work in progress'

Interferon-α

Interferon (IFN) is capable of inducing both haematological and cytogenetic remissions in CML, but the mechanism of action remains unclear. *In vitro*, IFN has a direct anti-proliferative effect on CML cells and improves defective adhesion; it may also act indirectly, enhancing immunosurveillance[4].

Although IFN can induce cytogenetic remissions in CML and improve survival, it is probably not 'curative'. It induces complete haematological and major cytogenetic (≤ 34% of Ph-positive metaphases) remissions in 7–81% and 0–44%, respectively[6]. Maximal response takes 9–18 months. Randomised controlled trials have demonstrated a survival advantage at five years (57% vs 42%) for IFN compared to hydroxyurea or busulphan[7]. However, many patients are intolerant to IFN: up to 60% require dose reduction due to side effects and 4–18% discontinue treatment[6]. Flu-like symptoms are common but relieved by paracetamol. Lethargy, anorexia, neuropsychiatric symptoms and exacerbation of autoimmune disease are well documented.

A recent randomised controlled trial[8] demonstrated higher haematological and cytogenetic remission rates with IFN combined with cytarabine. Three-year survival rates were also higher (85.7% vs 79.1%).

Allogeneic stem cell transplantation

Allogeneic SCT from a sibling or matched unrelated donor is currently the only potentially curative therapy. However, this is available to only 30% of patients[2] because many are considered unfit for transplantation, often due to advanced age, while others have no suitable donor. In this procedure, donor stem cells are either taken directly from bone marrow under general anaesthetic or from peripheral blood after granulocyte-colony stimulating factor priming. Transplant-related mortality is high (ca 20% and 40% for sibling and matched unrelated donor transplants, respectively), especially in the early post-transplant phase mainly due to acute graft versus host disease (GvHD). Bacterial, fungal and viral (particularly cytomegalovirus) infections also produce significant morbidity and mortality. Five-year survival for matched sibling transplants is 50–60%, and projected survival curves begin to plateau after 3–7 years[6]. Matched unrelated donor transplantation has a significantly poorer outcome: the US experience[9] of 1,423 matched unrelated donor transplants, median patient age 35 years, found 45-50% survival at three years. Outcome for all types of allografts is best in younger patients (<30 years old) in chronic phase at the time of transplantation and less than one year from diagnosis.

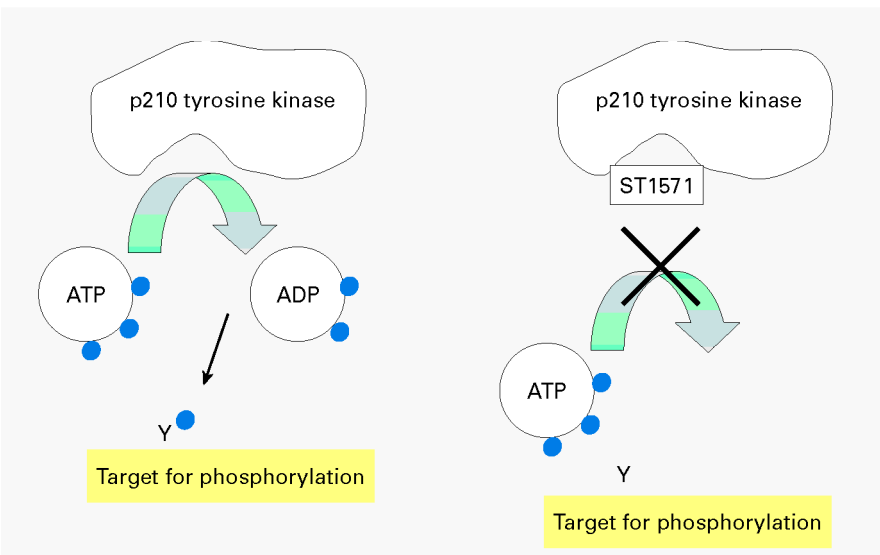
There has been no prospective randomised controlled trial of IFN versus allogeneic SCT in chronic phase CML. All comparisons are retrospective, and the data refer to unmatched populations, but there is agreement that IFN therapy offers better short-term survival and allogeneic SCT better long-term survival, with crossover 5–7 years after treatment[6].

Donor lymphocyte infusion and non-myeloablative transplantation

The curative effects of allogeneic transplantation are not solely due to disease ablation by high dose 'conditioning', followed by repopulation of the marrow by a 'clean' graft. The immune system plays a fundamental role. In the 1980s, donor marrow was T cell depleted to reduce the incidence and severity of GvHD. Although this was achieved, CML relapse rates increased to 60%, providing evidence for a graft versus leukaemia effect. Today, this effect is exploited by infusing donor lymphocytes to induce remission in patients relapsing after SCT.

Non-myeloablative transplantation aims to maximise the graft versus leukaemia effect whilst minimising procedure-related toxicity. After attenuated conditioning, stem cell infusion creates a chimera of donor and recipient marrow. Donor lymphocytes are then used to shift the equilibrium, over several months, in favour of donor cells and cure. Ideally, this reduces toxicity and acute GvHD, and may allow more

Fig 1. Mechanism of action of STI571. STI571 inhibits the binding of adenosine triphosphate (ATP) to the SH1 tyrosine kinase domain of *ABL*, thereby inhibiting phosphorylation and activation of downstream signalling pathways involved in leukaemogenesis. STI571 also inhibits the tyrosine kinase activity of the receptors associated with KIT and platelet-derived growth factor (ADP = adenosine diphosphate; black circles = phosphate groups; Y = tyrosine).



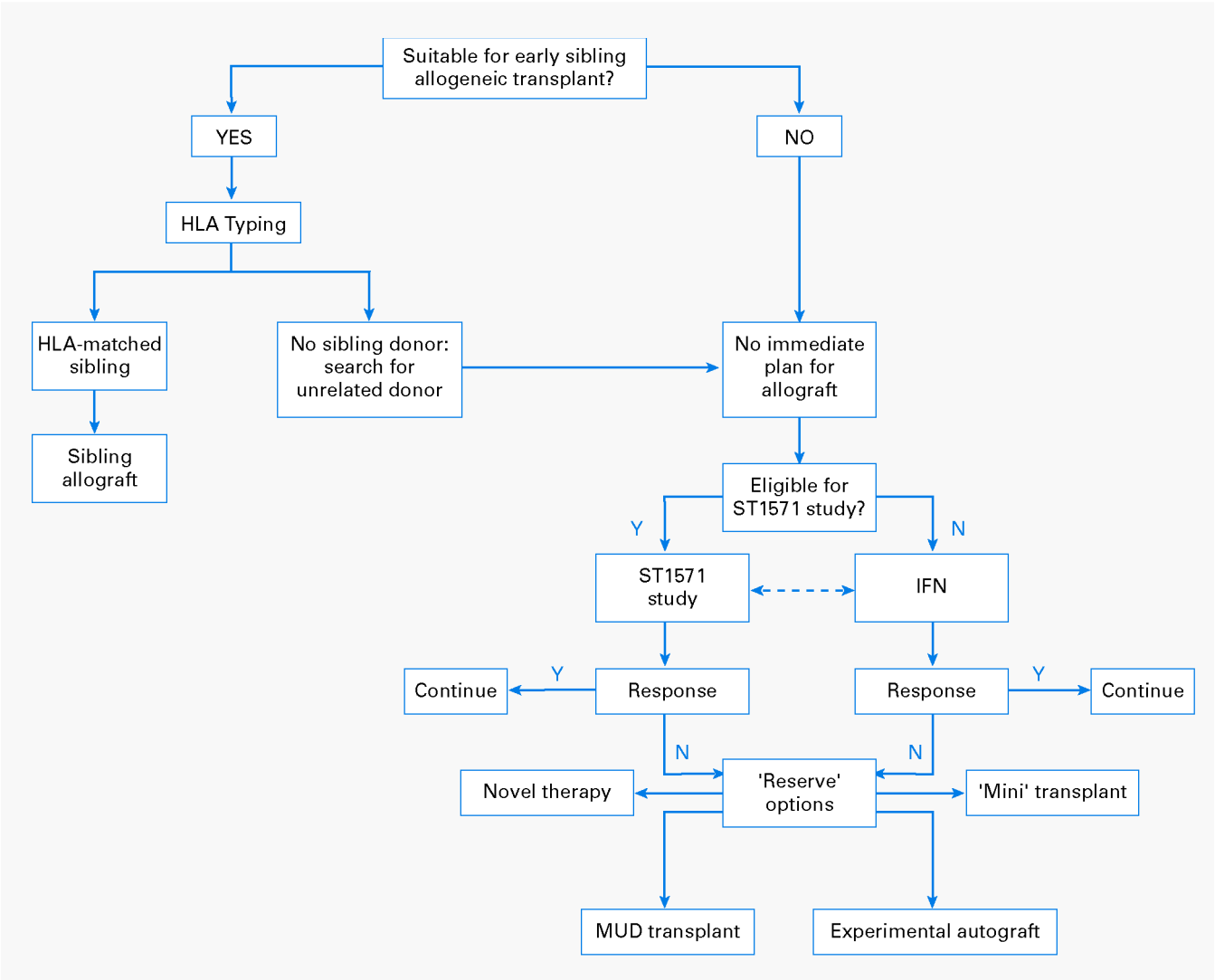


Fig 2. Possible treatment algorithm for a patient with newly diagnosed chronic myeloid leukaemia (IFN = interferon; MUD = matched unrelated donor; N = no; Y = yes).

patients to benefit from transplantation. Preliminary results are encouraging but more time is necessary for assessing CML relapse rates[10].

STI571: a tyrosine kinase inhibitor

STI571 (Glivec®), a new treatment in CML (first used in humans in June 1998), is designed to occupy the adenosine triphosphate binding site on the p210BCR-ABL fusion protein. STI571 blocks the dysregulated tyrosine kinase activity of the SH1 domain of the *BCR-ABL*-encoded fusion protein (Fig 1). Initial results are encouraging, with major cytogenetic remissions in 48% of patients resistant to IFN. STI571 is administered orally and has fewer side effects than IFN. The commonest problems are fluid retention, muscle cramps and rashes. (For key abstracts on STI571 presented at the American Society of Hematology 2000, San Francisco, see www.hematology.org/meeting/meeting00/abstractlist00.html.)

Other novel therapeutic agents

Polyethylene glycol (PEG) IFN is a modified IFN with a longer half-life than standard IFN, allowing once weekly administration. Some patients who fail standard IFN respond to PEG IFN, and it appears to have a favourable side effect profile.

Farnesyl transferase inhibitors are another group of signal transduction inhibitors. They prevent activation of some Ras proteins and show promise *in vitro*. A number of other signal transduction inhibitors are under development.

Management of advanced disease

Prognosis is very poor once blast crisis develops. Acute leukaemia chemotherapy regimens are administered.

There are more encouraging results in lymphoid than myeloid transformation (50% vs 20% return to chronic phase), but responses are rarely durable. Results of allogeneic SCT in blast crisis are also poor (five-year survival 0–10%). Encouraging responses to STI571 have been seen even in this poor risk group, though often of limited duration.

Summary

The therapy of CML is clearly 'work in progress'. Although long-term follow-up data for patients treated with STI571 are not yet available, preliminary results are encouraging. STI571 is likely to be licensed in late 2001/early 2002 and will certainly find a place in the treatment of CML.

Current therapeutic considerations are summarised in Fig 2. At all stages of treatment it is vital that the patient is fully aware of treatment options, their risks and benefits. In some cases there is little evidence to suggest that one treatment option is better than another; in these situations, treatment is likely to depend on a patient's individual circumstances and preferences.

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