Current use of imatinib in the treatment of chronic myeloid leukemia

Within the past 12-18 months increasing data have emerged regarding the role of imatinib in treatment of chronic myeloid leukemia (CML). However, despite impressive results in chronic phase CML, several major questions remain, including the durability of responses, whether cytogenetic and molecular responses are good surrogates for survival and whether we can do better than imatinib 400 mg as a single agent. In parallel, results from stem cell transplantation (SCT) continue to improve, rendering decision-making even more difficult for younger early chronic phase patients for whom this strategy could be an option.

Preliminary results of the IRIS study were recently presented at the annual meeting of the American Society of Hematology (ASH). This large randomized study compared imatinib with interferon and ara-C in newly diagnosed patients. For all parameters assessed, including cytogenetic response rates, progression-free-survival and tolerability, imatinib was clearly superior, establishing it as the new non-transplant therapy of choice. At 18 months major and complete cytogenetic response rates with imatinib were 85% and 74%, respectively. In contrast, less than 25% of interferon-treated patients achieved a major cytogenetic response. A survival advantage has not yet emerged but given the big difference in rates of transformation to advanced disease this seems likely in the near future. However, despite these encouraging response rates it is worth noting that only a small minority of patients (3%) achieved molecular negativity as assessed by quantitative reverse transcriptase polymerase chain reaction (RT-PCR).

So, can we do better than imatinib 400 mg daily as a single agent? Should we be using higher doses and should we add other agents to improve efficacy? Such modifications could further improve the rate and durability of complete cytogenetic responses by avoiding in vivo selection of resistant CML clones. Potential mechanisms of resistance could include kinase domain mutations (which have now been detected even prior to therapy in chronic phase patients), clonal evolution, Bcr-Abl gene amplification and Bcr-Abl positive stem cell quiescence. Preclinical data demonstrate that the addition of imatinib to other antileukemic agents, such as cytarabine, interferon, and daunorubicin, enhances the antiproliferative effect. Results from phase 1 and 2 studies combining imatinib with ara-C and interferon, in both standard and pegylated forms, as reported by Rosti et al. in this issue, show that this approach is feasible but there is as yet no evidence of improved efficacy over imatinib alone. Treatment is also more problematic with a higher incidence of myelosuppression and at this time is not recommended outside the setting of a clinical trial. There is tantalizing evidence that higher doses of imatinib may be superior. In the phase II pivotal study in accelerated phase, patients treated with 600 mg had better progression-free survival than those treated with 400mg. Kantarjian et al. at the MD Anderson Center have shown that dose escalation can overcome resistance in late chronic phase patients and finally, in newly diagnosed patients treated with 800 mg there was a trend towards higher cytogenetic response rates with over 80% of patients achieving major responses by 6 months with a complete response rate in almost two thirds of patients. Perhaps more significantly, the rate of molecular response was significantly higher than that seen with 400mg. Higher doses are associated with somewhat more toxicity in terms of fluid retention, gastrointestinal toxicity, cramps and myelosuppression. Clearly, the superiority of higher doses, as well as the role of combination therapy needs to be confirmed and a large international randomized study is planned. At present, allogeneic stem cell transplantation (SCT) is the only known curative treatment for CML as well as being the only treatment that induces molecular remission in a large number of patients. Based on published data, younger patients (less than 40 years of age) can expect a 70-80% chance of long-term disease-free survival with a matched related transplant. In this age group, results using molecularly matched unrelated donors are similar. Unfortunately, there remains a 10-20% risk of early death from treatment-related mortality even in the best risk patients and increasingly, patients in this situation are unwilling to accept these odds up front. While early transplantation is generally preferred, a delay of 1-2 years may not unduly compromise the chances of success from a subsequent transplant provided patients remain in chronic phase. Thus, an argument can be made for an initial trial of non-transplant therapy in many patients, reserving SCT for suboptimal responders. For example, the German CML study group compared the outcome of 103 patients treated with SCT with that of 196 patients treated with interferon as primary therapy. Patients were assigned to the different arms on the basis of donor availability (genetic randomization). Overall, treatment-related mortality was 29%. Survival at 4 years was superior on the interferon arm (81% vs 61%, p < 0.005). In low-risk (Euro score) patients, the respective figures were 91% versus 66%, p < 0.0007. The survival advantage for non-transplant therapy persisted for as long as 6 years.

The authors concluded that low-risk and possibly intermediate-risk patients should first be offered a trial of interferon and should be offered SCT only if
the response to interferon is unsatisfactory. Clearly, it would be desirable to be able to identify up-front those patients unlikely to respond to non-transplant therapies such as interferon and imatinib. Risk factors previously reported to have an impact on outcome with interferon therapy include clinical risk scores such as the Euro22 and Sokal scores,22 and 9q deletions.21 Until now, these had not been shown to predict responsiveness to imatinib. In this issue, Rosti et al. have demonstrated for the first time that responsiveness to an imatinib-based regimen is significantly related to the pre-treatment Sokal and Euro scores.13 These findings need to be confirmed in a larger set of patients, which should be possible through further analysis of the IRIS study. Pending the future widespread availability of more biologically based risk stratification, such as gene microarray and pharmacogenomic analysis, these simple risk scores will continue to be very useful in CML management.

The aim of treatment in CML is to reduce the number of Bcr-Abl-expressing cells to as low a level as possible. Thus, successful therapy should achieve, in consecutive order, a complete hematologic response, a cytogenetic response, and ultimately molecular remission, with no remaining evidence of Bcr-Abl transcripts by RT-PCR. Allogeneic SCT achieves all of these goals in the majority of patients; and although imatinib has achieved impressive cytogenetic responses, very few patients have achieved molecular negativity when sensitive, nested RT-PCR assays are used (Hochhaus A, personal communication). Whether achievement of molecular remission is necessary for long-term disease control in imatinib-treated patients remains an unanswered question. Achievement of a cytogenetic response is an important surrogate for survival in interferon-treated patients, and there is growing evidence that this is also the case with imatinib: lack of response being associated with disease progression.24

For these reasons, it is appropriate to repeat a bone marrow aspirate every 6 months after starting imatinib therapy. Samples should be sent for routine metaphase cytogenetics with or without fluorescent in situ hybridization. In addition to assessment of cytogenetic response (residual Ph positivity), metaphase analysis also allows detection of new clonal abnormalities in the CML clone, which may be associated with resistance and disease progression. We have reported that the presence of clonal evolution prior to therapy with imatinib results in inferior progression-free survival in patients with other accelerated phase features.25 In chronic phase patients treated with 400mg daily, clonal evolution was also associated with inferior outcome. However, in a small subset of late chronic phase patients with clonal evolution, treatment with 600 mg resulted in superior outcome: with a median follow-up of 12 months, the major cytogenetic response rate was 80% (12/15), with a complete cytogenetic response of 67% (10/15).25

None of these patients has relapsed. While this was a small study it does suggest that when patients with clonal evolution prior to imatinib are treated more aggressively, improved outcomes are possible. In this issue, Marktel et al. report their experience that development of clonal abnormalities while on treatment with imatinib is associated with subsequent disease progression, particularly in patients with recurrent imatinib-induced neutropenia.26 They hypothesize that these patients may have minimal residual Ph negative stem cells, leading to the selection by imatinib of a population of more transformed Ph+ cells, which are relatively resistant to the drug. In keeping with this, Hochhaus et al. recently reported the presence of clonal evolution in a significant number of patients with established resistance and showed that in some cases resistance occurred despite continuous inhibition of Bcr-Abl by imatinib.26 Marktel et al. conclude that the early identification of new clonal abnormalities may be an indication to adopt alternative therapeutic approaches.26

Once a patient has achieved a complete cytogenetic response, it is appropriate to monitor minimal residual status using quantitative RT-PCR for Bcr-Abl, when possible. Although still considered investigational and lacking standardization, this is a useful test. An advantage is that quantitative RT-PCR can be performed on peripheral blood, and rapid reduction in Bcr-Abl transcripts may predict subsequent cytogenetic response.27 Advocates argue that this test could replace the need for bone marrow examinations in the future. However, given the increasing reports of clonal abnormalities in Ph-negative cells in patients on imatinib (see also Marktel et al.), periodic monitoring of marrow metaphases is still warranted.28-31

While recognizing that these recommendations may evolve with time, at present one could consider an optimal response to be achievement of a complete hematologic response (CHR) within 3 months, a major cytogenetic response (MCR) within 6 months, and a complete cytogenetic response within 12 months. Absence of CHR by 3 months, lack of any cytogenetic response after 6 months or MCR after 12 months, or loss of CHR or MCR should all be considered indications for a change of therapy. In addition, a sharp rise in Bcr-Abl transcripts to a level consistent with genetic relapse could be considered an indication of treatment failure. Finally, the importance of adequate dosing of imatinib should be emphasized. Pharmacokinetic and response data indicate that 300 mg daily is the minimum effective dose, and generally speaking, dose
reductions below this level are not recommended.22 The judicious use of myeloid growth factors may reduce the frequency of treatment interruptions and maximize patients’ chances of response.23 For patients with established resistance, various methods to overcome resistance are being investigated. These include dose increases,19 the addition of conventional antileukemic agents and novel agents such as farnesyl transferase inhibitors, arsenic trioxide or decitabine.10,24 Consideration should also be given to allogeneic SCT in patients for whom this strategy is an option. In the future it is likely that monotherapy with imatinib will be replaced by double or even triple therapy combinations, combining imatinib with other non-cross-resistant agents, including new kinase inhibitors, mirroring the lessons learned in the treatment of tuberculosis and HIV.

While much has already been achieved, it is clear that much remains to be learned regarding the optimal use of imatinib. For this reason, patients and their physicians are strongly encouraged to participate in future clinical trials, which are essential to ensure further progress is made and enhance the long-term survival of our patients.

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References
2. Larsen RA, Imatinib (STI571) (Gleevec(TM)) as initial therapy for patients with newly diagnosed Ph positive chronic myeloid leukemia (CML) [abstract]; results of a randomized phase II study versus interferon-α. The IRIS (International Randomized IFN vs STI571) Study Group. Blood 2002;100:22a[abstract].
4. Hughes T, Kaela J, Brainford S. Molecular responses to imatinib (STI571) or Interferon + Ara-C as initial therapy for CML; results of the IRS study. Blood 2002;100:11a[abstract].
12. Mauro MJ, O’Dwyer ME, Stone RM. Preliminary evaluation of the combination of Imatinib mesylate (Gleevec) with low dose Ara-C as initial therapy for newly diagnosed chronic phase CML. Blood 2002;100:abstract.
Intense immunosuppression and autologous hematopoietic stem cell transplantation for multiple sclerosis

In this issue of Haematologica, Carreras et al. of the Hospital Clinic, Barcelona, Spain, report the results of a phase I–II study of high-dose immunosuppressive chemotherapy followed by infusion of autologous peripheral blood, CD34+ cell–selected, hematopoietic stem cells for the treatment of patients suffering from rapidly progressing multiple sclerosis (MS). This novel therapy, i.e. immunosuppression to the point of immune ablation and autologous stem cell transplantation (ASCT), was introduced for the management of autoimmune diseases (AD) about ten years ago and, although still not generally accepted, has been used in a considerable number of centers worldwide to treat patients with severe disease, not responding to conventional therapies. MS is a relatively common (1.2 cases per 1000 population), incurable, crippling disease caused by a T-cell–mediated autoimmune process against myelin in the central nervous system (CNS) with subsequent axon loss and gliosis. By 15 years from onset, half the patients have lost the ability to walk unaided. The main aim of the treatment is to prevent disability, that is to halt disease progression. Unfortunately, the two existing treatment modalities, i.e. immunosuppression with conventional-dose cytotoxic drugs and immunomodulation with interferon–α or copaxone, fail to control progressive disease. Mitoxantrone has recently been claimed to have meaningful effects, but the duration of this therapy is limited because of its cardiotoxicity. ASCT for MS was proposed in 1997. The study was based on the good results of syngeneic or pseudo-autologous transplantation in the control of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. High remission rates were attained when high-dose conditioning regimens were employed, while relapses depended on residual autoreactive cells surviving the conditioning, as well as on T-cells re-infused with the graft. How exactly ASCT can influence the course of EAE or MS is not fully resolved. There is an immediate beneficial anti-inflammatory effect in the CNS, due to the deletion of autoreactive clones, which can be easily attested by magnetic resonance imaging (MRI) and, possibly, by clinical improvement. ASCT has been shown to invariably suppress inflammation in the CNS to a degree which is not achieved by any other immunosuppressive therapy. This is in accordance with the well-known profound, and prolonged, immunosuppression observed after ASCT for malignant disease. Other therapies may also suppress inflammation in the CNS significantly, e.g. high-dose cyclophosphamide or the Campath–1H monoclonal antibody, but their effect is not durable. In addition, it seems that ASCT exerts not only immunosuppressive but also immunomodulatory activity. This has been demonstrated in cases of AD resistant to standard therapies, which became sensitive or could be managed with much lower drug-doses after transplantation. Tipping the immune balance towards suppressor mechanisms might explain this effect. A durable effect could also be expected from the possibility that ASCT could time-shift the autoimmune disease to an earlier, latent, phase and allow the immune system to develop from lymphoid progenitors by a process resembling normal ontogeny. There is still no proof, however, that transplantation can induce tolerance in this way. Another possible benefit is related to the capacity of stem cells to enter the CNS and transdifferentiate into microglia and neurons. In this way they could contribute to remyelination and neuronal repair, but this benefit is currently hypothetical.

Small scale phase I–II studies of ASCT for MS have been conducted since 1995. About 200 patients have been treated so far and more than two thirds of these have been reported to the Autoimmune Disease Working Party registry (ADWP) of the European Group for Blood and Marrow Transplantation (EBMT), which has published a comprehensive analysis of clinical outcomes in 85 rapidly progressing cases. The study showed the feasibility of the method, but also an associated mortality risk of about 6%, probably because of the inclusion of poor-risk patients. In terms of clinical efficacy, progression-free survival at three years was 74%, being higher for secondary progressive MS (78%) and for younger patients (89%). These probability rates are much higher than those achieved with any other, or placebo, therapy but, given the well–known difficulties in assessing MS patients neurologically, the clinical benefit of ASCT remains to be validated only in controlled trials. Individual centers participating in the