

Treatment of Chronic Myeloid Leukaemia Lessons and Challenges

John M. Goldman

Imperial College at Hammersmith Hospital, London, UK

Abstract

The choice of primary treatment for patients with chronic myeloid leukaemia diagnosed in chronic phase has become exceedingly difficult. There is little doubt that allogeneic stem cell transplantation (allo-SCT) can eradicate the leukaemia and that a 'graft-versus-leukaemia' effect makes a major contribution to this result; conversely only a minority of patients are eligible for transplant, which still carries an appreciable risk of mortality or protracted morbidity. For the majority of patients interferon-alpha prolongs life to some degree in comparison with hydroxyurea but is associated with considerable toxicity. The newly introduced tyrosine kinase inhibitor imatinib mesylate (imatinib, Glivec) induces complete haematologic remission in almost all cases and is associated with a very high incidence of cytogenetic response; its capacity to prolong life in comparison with interferon-alpha is not yet established. Here we review some factors that predict survival after non-transplant therapy and after allografting for CML in chronic phase. We consider two contrasting options for managing the newly diagnosed patient and conclude that for the present allogeneic stem cell transplantation soon after diagnosis should continue to be offered as an option for selected patients. Further experience with the use of imatinib as a single agent or in combination with other anti-leukemic agents may alter the picture in the near future.

1. Introduction

It is generally accepted that allogeneic stem cell transplantation (allo-SCT) has the potential to cure selected patients with chronic myeloid leukaemia (CML) and that cure depends on the contribution of a poorly defined 'graft-versus-leukaemia' effect [1]. However, there is a significant risk of morbidity or mortality as a direct consequence of the procedure. The introduction of interferon-alpha (IFN- α) in the 1980s complicated the decision whether or not to recommend allo-SCT and the early clinical experience with the Abl signal transduction inhibitor imatinib has made the decision making process yet more complex. Here we define the current problem in general terms and suggest some tentative recommendations. We recognize that these recommendations may be valid for only a limited period.

2. Predicting Survival with Non-Transplant Therapy

The duration of survival after diagnosis is highly vari-

able in a given cohort of patients with CML in chronic phase treated by non-transplant methods and the reason for this heterogeneity is largely unknown. Studies at the molecular or cytogenetic levels may have some prognostic value. For example, it was thought at one time that the precise position of the genomic breakpoint in the BCR gene might correlate with duration of survival but this notion has not been substantiated. Conversely recent data suggest that the presence of genomic deletions in the vicinity of the ABL-BCR gene on 9q+ may have prognostic significance [2]. Moreover the speed of telomere shortening in the leukemic clone may relate inversely to the duration of survival [3]. These last two findings need to be validated in larger clinical trials.

In the 1980s Sokal *et al* devised a staging system based on clinical and hematologic criteria at diagnosis that correlated with duration of survival for sub-groups of patients treated predominantly with busulfan [4]. (For individual patients the Sokal score can be calculated by accessing the website: <http://www.nrhg.ncl.ac.uk/cgi-bin/cml/sokal.pl>). More recently Hasford and colleagues in-

roduced an analogous system for predicting survival of patients treated with IFN- α [5]. (See: <http://www.pharmacoepi.de/cmlscore.html> for an on line calculator). Patients defined as 'low risk' patients treated with IFN- α had a median survival of 100 months while 'high risk' patients had a median survival of 45 months. This 'low risk' group of patients who may expect relatively long survival with IFN- α treatment are particularly difficult to advise regarding treatment options.

In practice one of the most effective ways of predicting survival is to assess the haematologic response to IFN- α at 6 months and the cytogenetic response at one year [6]. The greatest survival advantage is seen in IFN- α -treated patients who achieve a major cytogenetic response (<35% Ph positive metaphases), though the median time to optimal cytogenetic response may be one to two years. However, patients who do not achieve a complete haematologic response at 6 months or fail to achieve even a minor cytogenetic response (<65% Ph positive) at one year are unlikely to obtain a major cytogenetic response. Thus, patients not achieving these landmarks should be considered candidates for alternative therapies.

3. Trial of Therapy with IFN- α

It has been argued that low risk patients could safely be treated with IFN- α for the first year, particularly since the risk of blast transformation in these patients is 1-2%, even though they were otherwise eligible for allo-SCT. However, as patients transplanted within the first year of diagnosis have a lower transplant-related mortality than those transplanted at longer intervals [7], this strategy has been questioned in a decision-based analysis [8]. Moreover there has been much speculation that prior treatment with IFN- α might adversely affect the result of a subsequent allograft; in practice a carefully performed multi-center study in Germany implied that patients whose IFN- α treatment has been discontinued at least 90 days before allografting fare no worse than those who had never received IFN- α [9].

4. Predicting Survival after Allogeneic Stem Cell Transplantation

The range of possible outcomes for a patient undergoing allo-SCT varies widely. At one extreme a patient may have an uneventful post-transplant course and prove eventually to have been cured of CML. At the other extreme a patient may die within weeks of the transplant of acute graft-versus-host disease, opportunistic infection or other complications. Though the probabilities of complications and mortality can be estimated for given patient cohorts, there is no reliable way of predicting outcome for an individual patient.

Gratwohl *et al* made use of the data base maintained by the European Group for Blood and Marrow Transplantation (EBMT) to calculate a 'risk score' that gives a probability of survival post allo-SCT [10]. The risk score uses five specific pre-transplant features, phase of

CML, duration of disease, patient age, degree of donor/recipient histocompatibility and donor/recipient gender match. To this list may be added the CMV serostatus which correlates with survival, at least where the donor is not a family member [11,12]. Using the EBMT system transplant-related mortality for patients with total scores of 0 or 1 was approximately 20% while mortality rates were as high as 70% for patients with scores of 5 or 6. A similar analysis is currently being carried out by the International Bone Marrow Transplant Registry. This approach does not of course take into account the possible independent effects on transplant-related mortality of procedure-related factors, such as details of conditioning, stem cell dose or the approach used to prevent graft-versus-host disease.

The notion that a graft-versus-leukaemia effect plays a major role in leukaemia eradication has led to the introduction of 'reduced intensity conditioning' or 'non-myeloablative' stem cell transplants (NMSCT). In this procedure, the conditioning regimen is substantially reduced and reliance is placed on the donor-derived lymphocytes for eliminating the patient's leukaemia [13,14]. Theoretically this could greatly reduce the toxicity and mortality of the conventional procedure, thereby allowing allografting to be offered to a wider population of CML patients. Data from different centers using a variety of reduced intensity conditioning regimens show that some patients have achieved Ph-negativity. The rate of molecular negativity and the durability of these remissions will need to be determined from ongoing clinical trials before one can recommend that NMSCT, also referred to as mini-transplants, should replace conventional allografting procedures for patients deemed eligible for transplant.

5. Imatinib

Imatinib is an Abl-specific tyrosine kinase inhibitor capable of inhibiting the proliferation of CML cell lines and clonogenic CML progenitor cells [15]. It was first administered to CML patients in the summer of 1998 and further clinical trials accrued patients rapidly. The drug is given orally and is well tolerated with a manageable side effect profile. Of 54 patients with CML in chronic phase resistant or refractory to IFN- α treated with imatinib at a dose of 300 mg daily or greater almost all rapidly achieved complete hematologic responses; 17 (31%) achieved major cytogenetic responses and 7 (13%) complete cytogenetic remission [16,17]. Although the durability of these responses and the incidence of molecular remission cannot yet be assessed, an ongoing Phase II study of 532 chronic phase patients who failed IFN- α therapy was designed to address this issue. Thus the short term results suggest that imatinib is a major advance in comparison with the use of IFN- α or IFN- α plus cytarabine. This notion is currently being tested in an international prospective study in which 1106 newly diagnosed patients were randomized to receive either imatinib or IFN- α plus cytarabine. The incidence of complete cytogenetic remis-

sion at one year was much greater in the imatinib-treated patients than in the control arm (68% vs. 7%, $p < 0.001$) and the progression-free survival was also significantly better. Survival data cannot yet be assessed.

Although hematologic and cytogenetic responses to IFN- α have prognostic value, one cannot automatically assume that the same relationships will apply for imatinib. In other words, will the patient who obtains a good or complete cytogenetic response with imatinib survive as well (or better) than a patient who obtains a comparable response with IFN- α ? Will such responses be equally well maintained? Patients treated with IFN- α rarely achieve complete molecular remission when a sensitive reverse transcriptase polymerase chain reaction is employed [18]; will imatinib-treated patient do better in this regard? The ongoing randomized study comparing imatinib to IFN- α plus Ara-C is designed to address these questions and these data are essential before we can say with certainty that a particular patient treated with imatinib is likely to gain substantial prolongation of life.

The picture is complicated further by the fact that patients treated with imatinib in combination with other agents may survive longer than those treated with imatinib alone. There are plans to launch a 3-arm multi-centre study comparing imatinib with imatinib plus IFN- α and imatinib plus cytarabine in newly diagnosed patients, the co-called SPIRIT study. The number of possible permutations using other drugs is enormous. Moreover the results of allo-SCT could conceivably be improved by prior or subsequent use of imatinib. Conversely, as was required with IFN- α , it remains to be determined whether prior treatment with imatinib negatively impacts the survival from allo-SCT.

6. Patient Preference

In most cases the hematologist will be asked for his or her recommendation on primary management, although the preference expressed by the 'informed' patient must logically be the final deciding factor. For example, if the patient is determined to be cured of his or her disease, allo-SCT is currently the only approach clearly able to achieve this aim. Conversely a patient for whom an allo-SCT seems advisable may deem the risks of the procedure to be unacceptable and may thus prefer treatment with IFN- α or imatinib. These points notwithstanding, we suggest below a basis for treatment recommendations for individual patients.

7. Choice of Primary Therapy

There are two contrasting approaches to the management of the newly diagnosed patients with CML:

Option 1: One approach is to recommend that every newly diagnosed patient should receive initial treatment with imatinib, IFN- α or a suitable combination, ideally in the context of a clinical trial. Patients in the appropriate age range who 'fail' this trial of therapy and who have HLA-identical siblings or HLA-matched alternative

donors would then be offered an allo-SCT. The problems with this approach relate in part to the difficulty in defining a meaningful 'response' or 'failure' to imatinib (or the combination) and in part to the risk that the inherent delay might permit time for the disease to progress. Although it now seems unlikely that prior treatment with imatinib would adversely influence the results of a subsequent allograft, it is at least possible that a 'delay to transplant' might adversely affect the transplant result independently of any particular prior therapy.

Option 2: The second approach would be to try to decide within a few weeks of diagnosis whether a given patient was or was not a good candidate for allo-SCT. Newly diagnosed patients would likely fit into one of three categories: (a) Patients deemed eligible for a transplant. (For this purpose one must set an arbitrary level of risk of transplant related mortality above which an 'early' transplant should not be recommended; one might possibly accept a risk of up to 15 or 20%.) (b) Patients for whom a transplant is thought to carry a somewhat higher risk, and (c) Patients for whom a transplant could not reasonably be considered in any circumstance.

On this scheme patients in category (a) would proceed to transplant soon after diagnosis. Taking into account the various factors that impact on transplant-related mortality, one might assume that a patient under the age of 45 with an HLA-identical sibling donor or a patient under the age of 35 years with a molecularly matched volunteer donor might be a good candidate for an early allograft. One could speculate that these upper age limits for transplant might be reduced by 10 years for patients in the Hasford good risk category. For patients in category (b) it would be reasonable to offer a trial of therapy with imatinib or IFN- α and then to assess the response after 6 or 12 months. Patients who failed to achieve and maintain a reasonable degree of cytogenetic improvement would then be offered an allograft. Patients in category (c) might be offered primary treatment with imatinib or a combination of imatinib with IFN- α or cytarabine.

At the time of writing we believe the best advice for the newly diagnosed patient is Option 2 [19]. Relatively young patients with newly diagnosed CML who have HLA-identical sibling donors or molecularly HLA-matched unrelated donors should receive a conventional transplant within the first year of diagnosis. The role of NMSCT cannot yet be reliably assessed.

Although at present the curative potential of imatinib is unknown, it is entirely possible that imatinib alone, in combination with other agents or in conjunction with a novel approach to immunotherapy could eradicate CML. As clinical trials that test the various combinations will soon be initiated, patients not wanting to undergo allo-SCT should be encouraged to enroll in one or other of these studies. If one or two years from now it becomes clear that few if any of the patients responding to imatinib progress to advanced phase disease and that the cytogenetic responses achieved are durable, then Option

1 involving initial treatment with imatinib (or an imatinib-containing combination) will become the treatment of choice. This view will gain additional support if some of the patients who achieve complete cytogenetic responses also achieve durable molecular remissions.

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