

## \* CHAPTER 23

# HSCT for chronic myeloid leukaemia in adults

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## 1. Introduction

CML is a rare disease, since only 1 to 2 patients with CML are diagnosed per 100,000 population each year. In many aspects, however, CML is a disease with considerable historic significance in haematology, and in medicine in general. The discovery of the Philadelphia (Ph) chromosome in more than 90% of affected individuals led to the molecular characterisation of the disorder. The t(9;22) chromosomal abnormality results in the creation of the BCR-ABL fusion gene and the production of a deregulated tyrosine kinase. This in turn resulted in the identification of small molecules designed to inhibit the kinase activity and subsequently highly effective targeted therapy.

## 2. Role of imatinib therapy

Previously the only curative approach for patients with CML was allogeneic HSCT. For patients unsuitable for HSCT, interferon (IFN)- $\alpha$  with or without cytosine arabinoside (Ara-C) was considered the treatment of choice and was therefore selected as the standard arm in a phase III randomised study of the first tyrosine kinase inhibitor (TKI), imatinib (the IRIS study). Imatinib was superior to the combination of IFN+Ara-C in terms of haematological and cytogenetic responses, tolerability, and the likelihood of progression to accelerated phase (AP) or blast crisis (BC). After five years of follow-up only 7% of patients had progressed to accelerated-phase or blast crisis. Patients who had a complete cytogenetic response had a significantly lower risk of disease progression than did patients without a complete cytogenetic response. Grade 3 or 4 adverse events diminished over time, and there was no clinically significant change in the profile of adverse events (1). As a result imatinib has replaced IFN- $\alpha$  as first line therapy for CML (2).

As the haematological community has gained experience with imatinib, it has become clear that the majority of patients will have long-term benefit from imatinib alone. However a significant minority of patients (approximately 15–20%) will fail to achieve complete cytogenetic responses and a further proportion (15–20%) will lose these excellent responses (3). It would seem reasonable that allogeneic HSCT would be second line therapy for individuals intolerant to or failing imatinib. However the mechanisms of resistance to imatinib are currently the subject of considerable research activity and at least one of these has been elucidated. It would seem that leukaemic cells bearing point mutations in the tyrosine kinase domain can be present at diagnosis and/or emerge during treatment due to genomic instability. These mutations interfere with imatinib binding rendering the drug less effective. Several second generation tyrosine kinase inhibitors have subsequently been developed that are capable of inhibiting the great majority of the mutated kinases, including

dasatinib, nilotinib, bosutinib and Inno 406 (4). Phase I and II studies have confirmed the efficacy of these new TKIs in many patients with resistance or intolerance to imatinib, particularly if resistance occurs when the patients are still in the chronic phase (CP). The role of dasatinib and nilotinib in the management of CML has still to be defined and will be addressed in the next version of the recommendations of the European Leukaemia Net (ELN) and EBMT.

### 3. Role of HSCT

Any decision regarding the advisability of allogeneic HSCT must now take into consideration not only the factors long recognised to have prognostic value, i.e. age, disease phase, duration of disease, nature of stem cell donor and the genders of recipient and donor, but also the likelihood of response to first (and second) generation of TKIs. Within the EBMT recommendations for transplantation (5), allogeneic HSCT from sibling and well-matched unrelated donors remains a standard of care for the chronic and accelerated phases of the disease. In the past allografting has not been recommended for patients with blast crisis. However the introduction of imatinib has resulted in patients being referred for transplant at later stages in their disease and it is likely that this negative recommendation might have to be reviewed. It is possible that allogeneic HSCT in combination with second-generation drugs may offer these individuals better outcome. Autologous transplantation seemed to offer valuable prolongation of survival for selected groups of patients and was under investigation in randomised phase III studies at the time that imatinib became readily available. These studies were then unable to recruit sufficient numbers of patients and were closed prematurely. Appropriately this approach remains developmental according to EBMT recommendations (5).

#### 3.1. Autologous HSCT

The frequencies of autologous HSCT for CML have decreased considerably during recent years and currently fewer than 50 transplants per year are being reported to EBMT. Most of these patients are in acceleration or blast crisis. The rationale for autografting is to delay progression of disease and restore susceptibility to imatinib and/or IFN- $\alpha$ . In the past autologous transplant has involved the use of stem cell products heavily contaminated with leukaemic cells. The ability to achieve complete cytogenetic remission on imatinib has permitted the collection of stem cells with much reduced quantities of tumour and autologous transplant might find a role in disease management in the future. Stem cells harvested from patients in cytogenetic remission have been stored but few transplants have so far been performed.

### 3.2. Syngeneic HSCT

The results of syngeneic HSCT were evaluated recently by the EBMT. Excellent results were observed with an OS of 62% and a DFS of 32% at 20 years.

### 3.3. Allogeneic HSCT

HSCT remains the only curative treatment for CML. Since the advent of the TKIs, transplant rates have understandably decreased during recent years. However the outcome of allogeneic HSCT has in general improved over the same period of time (6). Patients with EBMT risk assessment scores of 0-2 (Table 1) (7) can expect 5 year overall survivals in excess of 85% so transplant remains an acceptable choice as upfront treatment for young patients with high Sokal and/or Hasford scores who are, in general, less likely to do well with imatinib. However the real controversy about allogeneic HSCT is whether this approach or a second generation TKIs should be the management choice for patients with imatinib resistance. At present the balance is in favour of HSCT for younger patients with HLA-identical sibling transplants but for older patients and younger patients without a donor the situation is less clear. On the one hand, the results of unrelated donor HSCT have improved considerably, reaching survivals similar to those seen in HSCT with related donors. On the other hand, the second generation TKI have reasonable efficacy and relatively low toxicity. It is entirely reasonable to attempt a short (say 3 months)

**Table 1: Risk factors for overall survival and transplant related mortality in CML**

	Risk factor	Score
Donor type	HLA-identical sibling	0
	Unrelated	1
Disease stage	First chronic phase	0
	Acceleration	1
	Blast crisis	2
Age of recipient at HSCT	<20 years	0
	20–40 years	1
	>40 years	2
Gender of donor and recipient	Other	0
	Male recipient/female donor	1
Time from diagnosis to HSCT	<12 months	0
	>12 months	1

trial of the second generation TKIs and to recommend transplant for those patients who have not shown an improvement in their cytogenetic responses. The method of transplant at this point remains wherever possible myeloablative. In elderly patients and in patients with concomitant diseases, reduced intensity conditioning transplantation offers an acceptable alternative. Reduced intensity conditioning procedures, perhaps with maintenance with a TKI and/or pre-emptive use of donor lymphocyte infusions, reduce the transplant related toxicity with compromising long term disease free survival (8), but are not ready yet to substitute conventional stem cell transplantation in eligible patients. To date, pre-transplant imatinib treatment has not been shown to have a negative effect on outcome after allo-HSCT.

#### 4. Monitoring response after allogeneic HSCT

Early data relating to the incidence and risk of relapse after allografting were derived from qualitative RT-PCR assays for BCR-ABL transcripts. However minimal residual disease (MRD) can be detected by RT-PCR for years post-transplant without progression and suggests that low levels of BCR-ABL transcripts identified some years after transplant for CML may not always herald relapse. The predictive value of MRD detection is strengthened by BCR-ABL quantification. Several studies have demonstrated that the molecular burden of BCR-ABL mRNA, and the kinetics of increasing BCR-ABL, predict relapse. A recent study from the Hammersmith has further attempted to quantify the risk of relapse (9). This group has defined disease recurrence as requiring intervention if the BCR-ABL/ABL ratio exceeded 0.02% on three occasions or reached 0.05% on two occasions. 243 patients were by serial quantitative RT-PCR and classified into 4 groups: 1) 36 patients were "durably negative" or had a single low level positive result, 2) 51 patients had more than one positive result but never more than two consecutive positive results ("fluctuating positive", low level (BCR-ABL/ABL ratio not satisfying definition of relapse) 3) 27 patients had persisting low levels of BCR-ABL transcripts but never more than three consecutive positive results ("persistently positive, low level") and 4) 129 patients relapsed. In 107 of these 129 relapse was based initially only on molecular criteria; in 72 (67.3%) patients the leukaemia progressed to cytogenetic or haematologic relapse either prior to or during treatment with donor lymphocyte infusions. The study not only confirmed the value of their definition of relapse but also indicated that the probability of disease recurrence was 20% and 30% in groups 2 and 3 respectively.

In view of the importance of the detection of residual disease at a time of low tumour burden when DLI are likely to be most effective, monitoring by RT-PCR is recommended at intervals no greater than three monthly for the first two to three

years post transplant, six monthly until 5 years after grafting and annually thereafter. Any patient with a positive result should be monitored more frequently (approximately 4 weekly) until the course of their disease can be defined more precisely. It is essential for each laboratory to establish their own quantitative definition of relapse as it is not possible to extrapolate the results achieved in one institution with those obtained elsewhere. This situation is unsatisfactory but will hopefully benefit from a global attempt at harmonisation of RT-PCR standards for the detection of BCR-ABL transcripts (10).

### 5. Treatment of relapse post-transplant

Donor lymphocyte infusions (DLI) have become the treatment of choice for patients who relapse after allogeneic SCT and durable molecular remissions are achieved in the majority of patients relapsing into chronic phase. In an EBMT study, survival after relapse was related to 5 factors: time from diagnosis to transplant, disease phase at transplant and at relapse, time from transplant to relapse and donor type (11). The effects of individual adverse risk factors were cumulative so that patients with 2 or more adverse features had a significantly reduced survival (35 vs. 65% at 5 years). Furthermore, DLI was less effective in patients who developed GvHD after transplant. However for patients transplanted in and relapsing in chronic phase the efficacy of escalating dose DLI was exceptionally high at >90% with a 5% procedural related mortality, rendering DLI the gold standard for the management of relapse in this group.

GvHD and marrow aplasia remain the two most important complications of DLI but when an escalating dose schedule is used these problems are greatly reduced. This has been shown recently in a large retrospective study conducted by the Chronic Leukaemia Working Party (CLWP) on 344 patients at 51 EBMT centres (12). Patients starting DLI with a dose of  $2 \times 10^7$  mononuclear cells/kg or less followed by escalating doses had less GvHD, less myelosuppression, the same response rate, better OS, better EFS, and less DLI-related mortality.

Imatinib is now an alternative to donor lymphocyte infusions as it could potentially be used to achieve remission without the risk of GvHD. It could also be effective when DLI has failed, and could be used in combination with lower doses of DLI to maximise responses whilst minimising the risk of GvHD. A number of groups have now used imatinib in the management of patients relapsing after allogeneic transplantation. Most of these patients were treated for relapse into advanced phase disease, as DLI are of limited value in this situation. Other patients were treated for cytogenetic relapse or haematological relapse into chronic phase, often in the presence of on-going immunosuppression for GvHD and/or after failure of DLI.

Recently, the Chronic Leukemia Working Party of the EBMT has reported a retrospective analysis of 128 patients treated with imatinib for relapse after allogeneic transplant (13). The overall haematological response rate was 84% (98% for patients in chronic phase (CP)). The complete cytogenetic response (CCR) was 58% for patients in CP, 48% for accelerated phase (AP) and 22% for patients in blast crisis (BC). Complete molecular responses were obtained in 25 patients (26%) of whom 21 were in CP or AP. With a median follow up of 9 months the estimated two-year survivals for CP, AP and BC patients were 100, 86 and 12% respectively. However Weisser et al. have recently compared the use of DLI or imatinib in 31 patients (14). 21 were treated for disease recurrence with DLI and 10 received imatinib because of lack of availability of the original donor. Molecular remissions were observed in 20 of the 21 patients (95%) who received DLI and 7 of 10 (70%) who were given imatinib. However 6 of the 10 patients treated with imatinib lost their best response whilst receiving the drug. Imatinib had been discontinued in 4 patients with confirmed molecular remission and disease recurred 2–4 months later in all but one of these individuals. 7 of the patients who failed imatinib subsequently received DLI and 6 achieved a molecular remission. Only 3 of the 20 patients who initially responded to imatinib experienced disease relapse. The authors concluded that imatinib, unlike DLI, cannot induce durable response in the majority of patients.

Of course future practice will involve patients who have received allo-SCT largely as a consequence of having failed imatinib and perhaps also second line TKIs. This will mean that the efficacy of targeted therapy for disease recurrence will have to be re-established.

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## Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

### 1. What is the only curative treatment for CML?

- a) IFN- $\alpha$  .....
- b) Imatinib .....
- c) IFN- $\alpha$  and Ara-C .....
- d) Haematopoietic stem cell transplantation .....

**2. Which factors are important for overall survival and transplant related mortality after SCT in CML?**

- a) Donor type, disease stage, age of recipient at HSCT, gender of donor and recipient and time from diagnosis to HSCT .....
- b) Donor type, age of donor at HSCT, gender of donor and recipient and time from diagnosis to HSCT.....
- c) Imatinib pre-treatment, disease stage, age of recipient at HSCT, gender of donor and recipient and time from diagnosis to HSCT .....
- d) Age of donor and recipient .....

**3. If a patient with CML in chronic phase has a syngeneic donor, would you consider:**

- a) A related non-syngeneic transplant, because of the unsatisfactory results of syngeneic HSCT.....
- b) A syngeneic HSCT.....
- c) An unrelated HSCT with an unrelated donor having a 10/10 match .....
- d) A cord blood HSCT.....

**4. At which time intervals and which response should be monitored in patients with CML after allogeneic HSCT?**

- a) Cytogenetics no greater than three monthly .....
- b) RT-PCR yearly .....
- c) RT-PCR no greater than three monthly.....
- d) RT-PCR no greater than three monthly and in case of positivity 4 weekly .....

**5. What is today the treatment of choice (gold standard) for patients who relapse after allogeneic HSCT?**

- a) Imatinib .....
- b) Donor lymphocyte infusion .....
- c) Dasatinib .....
- d) Nilotinib .....

## NOTES