Chapter 11

Bone Marrow Transplantation (BMT) in Philadelphia-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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Additional information is available at the end of the chapter

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1. Introduction

Ph+ ALL represents approximately about 25 to 40% of adults patients with ALL. In children, Ph+ ALL is much less common. Different breakpoint in the bcr gene, major and minor, produce fusion genes resulting in either a 210 or a 190 KDa protein respectively. It appears that major breakpoint fusion (p210) originates in hematopoietic stem cells whereas minor breakpoint fusion (p190) has a B cell progenitor origin, suggesting that p190 ALL and p210 Ph+ ALL may be distinct biological and clinical entities. [1] BMT is the first option for consolidation the complete remission in this patients. The proportion of patients able to undergo BMT in CR1 (Complete Remission) has increased with imatinib-based induction and early post-remission therapy, and there is currently no evidence that imatinib has an adverse effect on transplant-related morbidity or mortality (TMR). In addition, donor availability has benefitted from results showing equivalence of sibling and matched unrelated donors in terms of remission duration, non-relapse mortality and overall survival (OS).[1, 2] Several studies have shown improved post-transplant outcome of patients previously receiving imatinib-based treatment when compared with historic control groups, which have been dealt with in the previous chapter. As a consequence, most ALL study groups currently consider imatinib-based treatment, followed by matched related or unrelated allogeneic SCT (allo-SCT) in CR1, to be the gold standard of first-line therapy for Ph+ ALL. [3], Imatinib-based treatment not followed by SCT has been suggested to achieve OS and Disease Free Survival (DFS) similar to that obtained after SCT in one study, [4] and the results of MDACC study showed only a trend towards better OS in transplanted patients. [5] It still needs to be determined whether therapy based on second generation TKI may be equivalent or superior to BMT in a subset of patients, particularly those at high risk of TRM

The challenges in the treatment of Ph+ ALL are the selection of appropriate pre-transplantation therapy, the minimization of transplantation toxicity, the correct use of TKIs after transplantation and the appropriate use of and response to BCR/ABL monitoring.

2. Allogeneic stem cell transplantation with myeloablative conditioning

Attempts to improve outcome of Ph+ ALL included intensified conditioning regimens in order to reduce the relapse rate. An intensified preparatory regimen consisting of SCT after fractionated total body irradiation and Cyclophosphamide with or without etoposide has been explored by different investigation groups. Kröger et al investigated an intensified conditioning regimen including fractionated total body irradiation (TBI) (12 Gy), etoposide (30-45 mg/kg) and cyclophosphamide (120 mg/kg), followed by autologous (n = 5), allo-related (n = 13) or allo-unrelated (n = 6) bone marrow (n = 22) or peripheral stem cell (n = 2) transplantation in patients with Ph+ALL. One patient received busulfan (16 mg/kg) instead of TBI. Nineteen patients were transplanted in 1CR, two in 2CR, one in 1PR and two in relapse. After a median follow-up of 45 months, nine patients (37.5%) remain alive in CR. Nine patients (37.5%) relapsed and eight (33.3%) of these subsequently died. After autologous transplantation, four of five patients (80%) relapsed and died. In terms of late relapse the authors had seen it after allogeneic, as well as autologous transplantation, at 33 and 59 months, respectively. The Kaplan-Meier estimate of leukemia-free survival for all patients was 38% at 3 years and 35% at 5 years. For allogeneic transplants in first CR (n = 15) the estimate of DFS was 46% at 3 years and 34% at 5 years. Patients aged below 30 years had a better estimated OS at 3 years (61% vs 11%, $P < 0.001$). The bcr-abl fusion transcript (p210 vs p190 vs p210/190) did not affect DFS OR OS. For the authors an intensified conditioning regimen seems to improve the results of bone marrow transplantation in patients with Ph+ acute lymphoblastic leukemia. [6]

In another study Laport et al. evaluated sixty-seven patients with HLA-matched sibling donor who received fractionated total body irradiation (FTBI) and high-dose VP16, whereas 11 patients received TBI/VP16/cyclophosphamide, and 1 patient received TBI/VP16/busulfan. The median age was 36 years. At the time of BMT, 62% of the patients were in first complete remission and 38% of the patients were beyond CR1 (> CR1). The median follow-up was 75 months The 10-year OS for the CR1 and beyond CR1 patients was 54% and 29%, and event-free survival was 48% and 26%. The authors did not find significant difference in relapse incidence (28% vs 41%, but non relapse mortality was significantly higher in the beyond CR1 patients, (31% vs 54%). In this study the univariate analysis, factors affecting event-free and overall survival were white blood cell count at diagnosis (< 30 _ 109/L vs > 30 _ 109/L) and disease status (CR1 vs > CR1). The median time to relapse for CR1 and for beyond CR1 patients was 12 months and 9 months, respectively. These results showed that FTBI/VP16 with or without cyclophosphamide confers long-term survival in Ph+ ALL patients and that disease status at the time of BMT is an important predictor of outcome. [7]

In these and other studies the factors that identify modifications in the transplant outcome have been analyzed. Complications such as TRM was mainly due to infections or GVHD (graft-

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versus-host-disease), and was higher in patients with more advanced disease. Factors affecting event-free and overall survival likewise included disease status (CR1 vs > CR1) and higher age, with a cutoff at approximately 30 years, at the time of transplantation. [8] The intensified preparatory regimens confer long-term survival in a subset of patients with Ph+ ALL, relapse and TRM remain important causes of treatment failure, making success unlikely in patients with more advanced disease. Interestingly, comparable survival data were reported for patients with high-risk ALL with the Philadelphia chromosome and those with normal cytogenetic; actuarial disease-free survival (DFS) at 5 years was 43% for patients in first remission. Chronic GVHD appears to reduce the risk of relapse without increasing the risk of TRM, whereas severe acute GVHD increases the risk of TRM without diminishing the risk of relapse. Thus, patients who developed extensive chronic GVHD had better survivals, and those who developed grade III-IV acute GVHD had worse survivals than did the others. [8,9]

3. Reduced-intensity conditioning allogeneic stem cell transplantation

In order to decrease the high TRM associated with myeloablative allogeneic stem cell transplantation but still generate a graft-versus- leukemia effect (GVLE), reduced-intensity conditioning (RIC) regimens were developed for patients unlikely to tolerate the toxicities of intensive preparative regimens. Overall, several retrospective analyses and a single prospective study suggest that BMT with RIC is feasible in adult patients with high-risk ALL but associated with a high probability of treatment failure in patients transplanted beyond CR1. [10,11,12,13] Myeloablative BMT carries considerable risk of TRM and is not applicable to older individuals. Opinions vary on the upper age limit for the procedure; in UKALL12/E2993, a very high TRM of nearly 40% was observed in patients older than 35 years of age receiving myeloablative BMT, resulting in a protocol limit of 40 years of age in the current UK NCRI study, UKALL14. In some studies, patients are offered myeloablative BMT up to the age of 55 years. [14] There are several studies that show the results of the regimens of reduced intensity but with different results, selection and design which must be interpreted with caution.

A comparative study of European Group for Blood and Marrow Transplantation (EBMT) registry report one retrospective study where the outcome of 576 adult acute lymphoblastic leukemia patients aged > 45 years, and who received a reduced-intensity conditioning (RIC; n=127) or myeloablative conditioning (MAC; n=449) allogeneic stem cell transplantation from a human leukocyte antigen-identical sibling while in complete remission is assessed. With a median follow-up of 16 months, at 2 years, the cumulative incidences of non-relapse mortality and relapse incidence were 29% (MAC) versus 21% (RIC), and 31% (MAC) versus 47% (RIC), respectively. In a multivariate analysis, nonrelapse mortality was decreased in RIC recipients, whereas it was associated with higher relapse rate. At 2 years, LFS was 38% (MAC) versus 32% (RIC). In multivariate analysis, the type of conditioning regimen (RIC vs. MAC) was not significantly associated with leukemia-free survival. For this authors the RIC allo-SCT from a human leukocyte antigen identical donor is a potential

therapeutic option for acute lymphoblastic leukemia patients aged > 45 years in complete remission and not eligible for MAC allo. [15]

The RIC approaches should be vigorously pursued as part of prospective studies in order to define their role in ALL. In Ph^+ ALL in particular, inquiry into the role of TKIs after alloHSCT is vital. The forthcoming study from the UK NCRI, UKALL14, assigned all patients with ALL of 40 years of age or more to a nonmyeloablative approach with fludarabine, melphalan, and alemtuzumab in an attempt to obtain good disease control with less GVHD. [14] The incidence of TRM and disease progression in these studies was still substantial, however particularly in patients transplanted beyond first CR. The incidence of acute (grades II-IV) and chronic GVHD (43.2% and 65.6%, respectively) was high, but the significantly lower frequency of disease progression in patients with cGVHD highlights the antileukemic activity of cGVHD [15]

4. Autologous stem cell transplantation

The role of autologous stem cell transplantation (ASCT) was studied most extensively in the pre-imatinib era and has attracted little interest since then. While there are no prospective, randomized trials comparing autologous and allogeneic SCT, treatment outcome with conventional ASCT procedures has consistently been inferior to BMT in several retrospective analyses due to a high relapse rate. More recently, some investigators have reevaluated the therapeutic potential of ASCT when given in conjunction with TKI. Shin et al. describe an approach in which Ph+ ALL patients receive imatinib as interim therapy between chemotherapeutic cycles and prior to autologous SCT, followed by maintenance therapy. Small patient numbers and as yet limited duration of follow-up preclude a definite assessment of this strategy, which can be expanded to include the more potent second-generation TKI. [15, 16]

5. Imatinib after SCT

A very important and as yet unanswered question concerns whether TKIs should be administered after BMT and under what circumstances. The high risk of relapse in patients who are MRD positive after SCT makes administration of an ABL-directed TKI conceptually attractive as a measure to prevent relapse and reestablish molecular negativity. [17] Administration of imatinib early after HCT was tested by Carpenter et al in 22 patients, 15 with Ph+ ALL and 7 with high-risk chronic myelogenous leukemia, (CML) who were enrolled in a prospective study and given imatinib from the time of engraftment until 365 days after HCT. Before day 90, adults (n =19) tolerated a median average daily imatinib dose of 400 mg/d, and children (n = 3) tolerated 265 mg/m2/d. The most common adverse events described by the authors were related to imatinib administration with grade 1-3 nausea, emesis, and serum transaminase elevations. [18]

The positive minimal residual disease (MRD) after stem cell transplantation: is associated with a relapse probability exceeding 90%. Starting imatinib in the setting of MRD may decrease this

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high relapse rate. This hypothesis was evaluated in another prospective study by Wassmann and al. in 27 Ph+ALL patients that received imatinib upon detection of MRD after SCT. Bcr-abl transcripts became undetectable in 52% of the patients, after a median of 1.5 months, (they called $^{early}CR_{mol}$). All patients who achieved an $^{early}CR_{mol}$ remained in remission for the duration of imatinib treatment; 3 patients relapsed after imatinib was discontinued. The failure to achieve polymerase chain reaction (PCR) negativity shortly after starting imatinib predicted relapse which occurred in 12 of 13 patients after a median of 3 month. The DFS in $^{early\text{-}}CR_{mol}$ patients was 91% and 54% after 12 and 24 months, respectively, compared with 8% after 12 months in patients remaining MRD+. Thus in the post-transplant setting, the molecular response to imatinib discriminates between patients with long-term DFS and patients likely to experience relapse and who therefore should receive additional or alternative antileukemic therapy. [19]

Burke et al between 1999 and 2006, in a single-center analysis of 32 patients with Ph+ ALL, including pediatric patients, who underwent allo-HCT and received imatinib in either the pre- or post-transplant period. The median age at HCT was 21.9 years, of 32 patients, 15 received Imatinib therapy pre- or post-HCT (imatinib group) and 17 patients received either no imatinib (n=11) or only after relapsed (n=6) (non imatinib group) There was a trend towards improved OS, relapse-free survival and relapse at 2 years was, 61%, 67% and 13% for the imatinib group (n = 15) as compared with the 41%, 35% and 35% for the non-imatinib group (n = 17), respectively. Cardiac toxicity and TRM at 2 years were similar between the groups. [20] Overall, further data is needed to define the optimal use and impact of imatinib in the peri-transplant management of patients with Ph+ ALL.

6. Monitoring of *BCR-ABL* in Ph$^+$ ALL

Real-time PCR *BCR-ABL* quantification is often used to monitor minimal residual disease in patients with Ph$^+$ ALL, but optimal practice and interpretation of results is unclear. In addition, while there is considerable standardization of methodology for p210 quantification, there is less standardization than for p190 quantification.[17] There are conflicting reports on the association between an initial decrease in *BCR-ABL* transcript level and long-term outcome. Preudhomme C et al. In the "pre-imatinib" era, have observed a good correlation between *BCR-ABL* transcript levels and the outcome which had been reported in 17 patients with Ph +ALL. [21]

Ottmann et al. analyzed in elderly patients with de novo Ph+ALL who were randomly assigned to induction therapy with either imatinib Ind(IM)) or multiagent, age-adapted chemotherapy Ind(chemo). Imatinib was subsequently co-administered with consolidation chemotherapy. The *BCR-ABL* transcript levels have also been correlated with response. [22] Unlike in chronic myeloid leukemia, there is no consensus on what represents an optimal response.

Lee et al were able to demonstrate that a 3-log reduction in *BCR-ABL* transcripts after 1 month of imatinib treatment strongly predicted a reduced relapse risk. The outcomes were evaluated

for Ph+ ALL in 23 adults patients in remission treated with allogeneic bone marrow transplantation (BMT) [23]

In contrast to the data published by these authors, Yanada et al observed no association between rapid achievement of *BCR-ABL* negativity and long-term outcome after an initial imatinib/chemotherapy induction regimen in 100 patients with Ph+ ALL treated and MRD monitoring [24]

Pfeifer et al examined the prevalence of KD mutations in newly diagnosed and Imatinib-naïve Ph+ ALL patients and assessed their clinical relevance in the setting of uniform frontline therapy with imatinib in combination with chemotherapy. The German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) trial ADE10 for newly diagnosed elderly Ph+ ALL were retrospectively examined for the presence of BCR/ABL KD mutation by denaturing high-performance liquid chromatography (DHPLC),cDNA sequencing and allele-specific polymerase chain reaction (PCR). A KD mutation was detected in a minor subpopulation of leukemic cells in 40% of newly diagnosed and imatinib naïve patients. At relapse the domin cell clone harbored an identical mutation in 90% of the cases, the overall prevalence of mutations at relapse was 80 %. P loop mutations predominated and were not associated with an inferior hematologic or molecular remission rate or shorter rmission duration compared with unmutated BCR/ABL. BCR/ABL mutations conferring high level imatinib resistance are present in a substantial proportion of patients with de novo Ph+ ALL and eventually give rise to relapse.[25]

Soverini et al. analyzed samples collected at diagnosis from 15 patients with Philadelphia-positive acute lymphoblastic leukemia who subsequently received tyrosine kinase inhibitor therapy (dasatinib) by cloning the BCR-ABL kinase domain in a bacterial vector and sequencing 200 independent clones per sample. Mutations at relatively low levels (2-4 clones out of 200) could be detected in all patients--eight who relapsed and seven who achieved persistent remission. Each patient had evidence of two to eight different mutations, the majority of which have never been reported in association with resistance to tyrosine kinase inhibitors. They suggest that the BCR-ABL kinase domain is prone to randomly accumulate point mutations, although the presence of these mutations in a relatively small leukemic subclone does not always preclude a primary response to tyrosine Kinase inhibitor. [26]

So much imatinib or dasatinib regimens can be achieving complete clinical response in 95 -100% of patients.

Eligible patients will be treated with alloHSCT wherever possible, and for these patients, *BCR-ABL* monitoring early in the course of the disease is unlikely to change practice at present. For patients not receiving alloHSCT, serial monitoring during initial therapy is of more relevance because it might prompt a switch of therapy before hematological relapse. [17]

At present, the evidence suggests that *BCR-ABL* by RTQ-PCR should be monitored and must be combined with screening for BCR/ABL domain mutations (in case of suspected resistance) after alloHSCT and that reemergence of *BCR-ABL* is a rational basis for intervention. [27]

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7. Resistence

Approximately 80 %to 90% of patients with Ph+ ALL who relapse while on imatinib are found to have BCR/ABL mutation with predominance of P-loop and T315I mutations. With dasatinib relapse is most frequently associated with T315I mutation, whereas P-loop mutations are less common. [28] With variable frequency, the mutations can be present at the time of diagnose. Pfeifer et al detected low levels of mutations in pretreated patients with imatinib with Ph+ ALL who, at the time of relapse, presented the same mutated dominant clone in most of the cases. Soverini et al also reported a high frequency of BCR/ABL mutations which were lately found at the time of relapse. [25,26] Mutations can also be acquired or emerge under the selection pressure of TKI treatment.

Other additional mechanisms of resistance to therapy with TKI have also been suggested, such as cytogenetic abnormalities in addition to Ph chromosome which are present in approximately one third of cases of adult leukemia and have been associated with inferior outcome. Members of the SRC family of kinase have been implicated in leukemogenesis and in the development of imatinib resistance in BCR/ABL positive ALL, suggesting that simultaneous inhibition of Src and Bcr/Abl kinases may benefit individuals with Ph+ acute leukemia. [29, 30]

8. Relapses in Ph+ acute lymphoblastic leukemia

Relapsed ALL is a clinical problem, and outcomes are extremely poor. Fielding et al in the UKALL12/ECOG study, examined 609 adults with recurring ALL, where the OS of newly diagnosed patients was 38% at 5 years, OS at 5 years after relapse was 7%. [31] The CR2 is possible in only ~ 50% of chemotherapy-treated patients. Many young patients with Ph^+ ALL will have already received alloHSCT, making salvage harder and with more toxicity, particularly if chemotherapy reinduction is under consideration. Nevertheless a phase 2 study of dasatinib 140 mg/d in patients who relapsed after imatinib-containing regimens demonstrated that approximately half of the patients could achieve a CR2 with modest toxicity. However, median remission duration was only 3.3 months. Under these circumstances, a second allo-HSCT might be considered.[32] Ishida et published case report which shows a positive outcome for a patient who received dasatinib followed by a RIC alloHSCT after imatinib and myeloablative allo-HSCT which failed to control the disease. All reports of allo-HSCT show less than an ideal outcome in patients beyond CR1. However, many of these were reported before the advent of TKIs, which might, in selected circumstances, allow for second definitive transplantation procedures [33] Among the strategies to treat Ph + ALL relapse after Allo-SCT we will mention donor lymphocyte infusion. This treatment seems to be effective in CML, but it is less useful in ALL maybe due to the immune escape mechanisms of the blastic cells. Likewise, the addition of chemotherapy to ILD is not associated with a better prognosis.

Immunotherapy with donor lymphocyte infusion (DLI) and imatinib appears to be well tolerated but it is rarely and in general only transiently effective. A rationale for the combined

use of DLI and second-generation TKIs such as nilotinib is suggested by case reports, but prospectively collected data are as yet not available. [34]

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