Chronic Myeloid Leukemia

Imatinib preceding allogeneic stem cell transplantation in chronic myeloid leukemia

In 37 adults with chronic myeloid leukemia undergoing allogeneic stem cell transplantation imatinib prior to transplant had no discernible negative impact on 100-day mortality (13%) and severe acute (22%) or extensive chronic graft-versus-host disease (31%). After a median of 203 days (range: 18-1419) overall and progression-free survival rates are 62% and 54%, respectively.

Haematologica 2006; 91:1145-1146
(*http://www.haematologica.org/journal/2006/08/1145.html*)

Imatinib is a potent inhibitor of *BCR-ABL*[1] and induces hematologic and cytogenetic responses in patients with chronic and advanced phases of chronic myeloid leukemia (CML).[2] The majority of CML patients receive imatinib as first-line therapy.[3] Despite the high efficacy of imatinib, allogeneic stem cell transplantation (SCT) is regarded as the only way of achieving a permanent cure but, in contrast to imatinib, is associated with considerable treatment-related mortality.[4] A possible therapeutic strategy is based on testing the response to imatinib before deciding whether to perform allogeneic SCT. Thus, it is becoming more common to see patients who are offered a transplant after exposure to imatinib with the potential risk of increased transplant toxicity and effects on outcome.

We retrospectively analyzed engraftment rate, incidence of acute and chronic graft-versus-host disease (GvHD), transplant-related mortality and survival in 37 adults with CML, who received imatinib with the aim to achieve remission in first chronic phase or advanced phases (accelerated phase, blast crisis) and subsequently underwent allogeneic SCT from sibling or volunteer unrelated donors. The decision to proceed with allogeneic SCT was based either on relapse or failure to achieve remission or, in younger patients in cytogenetic remission, on an individual decision in case of donor availability. In a sibling donor setting serological human leukocyte antigen (HLA-A, -B, -Cw, -DRB, -DQ) typing was performed. In the unrelated donor setting HLA-A, -B, -Cw, -DRB1 were typed at a molecular level and HLA-DQ at a serological level. Transplant conditioning consisted of fractionated total body irradiation [TBI: 13.2Gy (sibling donor), 14.4Gy (unrelated donor)] and 120 mg/kg cyclophosphamide. Thirty-one recipients of transplants from unrelaetd donors received *in vivo* T-cell depletion with alemtuzumab (anti-CD52, 30 patients) or anti-thymocyte globulin (1 patient). GvHD prophylaxis consisted of cyclosporine A and methotrexate.

The patients' characteristics, response to imatinib and transplant details are summarized in Table 1. Seventeen patients responded to imatinib, but 20 had primary or secondary resistance to this drug. No *ABL*-kinase mutations were found at treatment initiation. In two patients mutations (G250E and M244V) were detected at the time of imatinib resistance, both patients relapsed after transplantation. Eighteen patient/donor pairs were HLA-matched (10/10), whereas in 19 mismatches were accepted: HLA-Cw (n=5), molecular HLA-A, or -B, or -DRB1 (n=11), serological HLA-A or -B (n=3). Engraftment failure occurred in 2.7%. The probability of transplant-related mortality on day 100 was 13%. The causes of early deaths were veno-occlusive disease (n=1) infections related to GvHD (n=2) or without GvHD (n=2). The rate of GvHD grade III-IV was low at 22%. Extensive chronic GvHD occured in 31% of evaluable patients. T-cell depletion with alemtuzumab (30 patients) may have contributed to the low GvHD rates. The non-relapse mortality increased to 32% at 1 year due to graft failure (n=1), infections related to GvHD (n=1), and infections without GvHD (n=5); however, non-relapse mortality was not correlated with the dose or duration of imatinib treatment. The probability of overall survival was significantly (p<0.0001) better in 11 patients transplanted in first chonic phase (100%, median follow-up 724 days, range 100-935 days) than in 26 patients transplanted in advanced phase (46%, median follow-up: 151, range 18-1419 days). Survival of patients transplanted in second chronic phase was poor (25%) compared to that of patients transplanted in first chronic phase (100%) and accelerated phase (53%). The probability of progression-free survival, defined as survival with no evidence of molecular progression by real time quantitative poly-

Table 1. Patients' characteristics and treatment summary.

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Gender: Male/female	23/14
Patient age: median (range) in years	31 (16-55)
Disease status at diagnosis:	n
CML in first CP	20
CML AP or BC	11/6
Duration of imatinib treatment: median (range) in months	8.5 (1-31)
Imatinib dose: mg per day	n
200/400/600/800	1/14 /20/2
Time from imatinib discontinuation to transplant: in weeks	n
< 2/2 to 8/> 8	20/6/11
Response to imatinib (17 patients):	n
major molecular/major cytogenetic/	2/8/4/3
minor or minimal cytogenetic/complete hematologic	
Resistance to imatinib (20 patients):	n
primary/secondary	15/5
Treatment in patients with initial (6 patients)	n
or secondary BC (3 patients):	
Imatinib only/two courses of FLAG or	
Ida-FLAG/one course of DA and one course of MAE	4/4/1
Treatment response in patients with BC (9 patients):	n
response to Imatinib only/response to chemotherapy	
/refractory to chemotherapy	4/4/1
Time from diagnosis to transplant in months:	
< 12 months/> 12 months	11/36
Time from diagnosis to transplant:	
median (range) in months	19 (4-96)
Disease status at transplant:	n
CML in first CP	11
CML in AP/BC/2nd CP	17/1/8
Donor type: sibling/unrelated donor	5/32
HLA match 10/10: full match/mismatch	18/19
Donor gender match: matched/male recipient	
female donor/female recipient-male donor	22/8/7
Patient CMV status: negative/positive	22/15
Patient and donor CMV status: negative in both/other	15/22
Stem cell source: bone marrow/peripheral blood	26/11

HLA: human leukocyte antigen; CMV: cytomegalovirus; FLAG: chemotherapy with fludarabine, cytarabine and granulocyte colony-stimulating factor G-CSF; Ida-FLAG: chemotherapy with idarubicin and fludarabine, cytarabine and granulocyte colony-stimulating factor (G-CSF); DA: chemotherapy with daunorubicin and cytarabine; MAE: chemotherapy with mitoxantrone, cytarabine and etoposide.BC: blast crisis; CP, chronic phase; AP, accelerated phase

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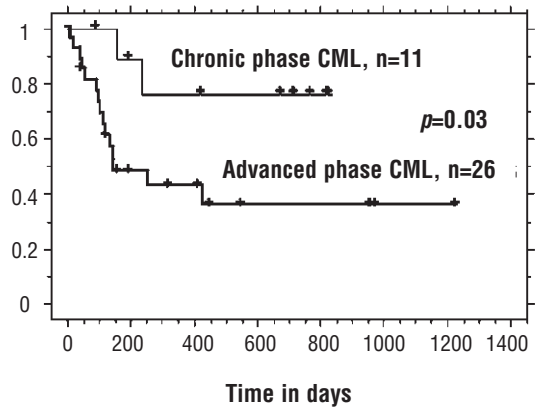

Figure 1. Probability of progression-free survival after allogeneic stem cell transplantation.

merase chain reaction, was significantly higher (p=0.03) in first chronic phase group (81%, median follow-up 335, range 100 – 837 days) than in the advanced phase group (33%, median follow up 150, range 18–1238 days), as illustrated in Figure 1. In univariate analysis negative cytomegalovirus serology of both recipient and donor had a positive impact on overall survival (p=0.04), whereas age, donor type, stem cell source, HLA match, time from diagnosis to transplant, use of T-cell depletion, dose and duration of imatinib treatment and response to imatinib had no impact.

Previous reports of patients with CML in blast crisis and Philadelphia-positive acute lymphocytic leukemia treated with imatinib prior to SCT showed no negative impact of imatinib on outcome.[5,6] Results of a recent multi-center analysis of 61 patients treated with imatinib prior to SCT[7] showed a relatively high rate of 100 day non-relapse transplant-related mortality (30%) and low overall (37%) and progression-free survival (33%). Our results on outcome after allogeneic SCT at a single center show low rates for transplant-related mortality, engraftment failure and GvHD. Survival in this group is at least as good as that of historical from the pre-imatinib era in first chronic phase (overall and progression-free survival 61% and 36%, respectively),[8] and in advanced phase patients (overall survival 37.6%),[9] indicating that the sequential approach is feasible.

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Key words: imatinib, CML, allogeneic stem cell transplantation.

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