Therapeutic Choices in Patients with Ph-Positive CML: SCT or TKI ?

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Abstract

Background: CML is a hematopoietic stem cell disorder which constitutes a clinical model for molecular detection and therapy as characterized by the reciprocal translocation t(9;22) resulting in Bcr/Abl oncogenic fusion gene or the Philadelphia chromosome (Ph) which is expressed as a fusion protein with deregulated tyrosine kinase activity that has been recognized to play a key role in the pathogenesis of the disease 1. The only proven curative therapy for CML is allogeneic stem cell transplantation (allo-SCT), however; this approach is available for only less than 40% of patients who have an HLA matched donor 2.
The introduction of imatinib mesylate (IM) in 1998 has revolutionized the management of CML. The drug is a potent and selective tyrosine kinase inhibitor 3 which acts by occupying the ATP-binding site of the ABL tyrosine kinase component of the BCR-ABL oncoprotein and maintains it in an inactive conformation. It offers excellent short-term results, but without long-term follow-up 4.
However this line of treatment requires tremendous resources and it becomes increasingly difficult for hematologists practicing in the developing world to reconcile the difference between what is possible and what is available.

Aim: We retrospectively reviewed the different treatment options that were offered to our CML patients during the last decade.

Patients and methods: A total of 377 patients with Ph-positive CML in first chronic phase were followed during the past 11 years in Nasser Institute hospital for research and treatment and in the National Cancer Institute , NCI , Cairo university.
Among them, 268 were given myeloablative allogeneic SCT, 18 were given a reduced –intensity transplant and 91 patients received imatinib as frontline treatment.

For the allogeneic transplant group follow up chimerism analysis and PCR for Bcr/ Abl were performed at regular intervals and whenever necessary.
For the imatinib group, RT- QPCR was performed at regular intervals every 3 months during the whole follow-up. Conventional karyotyping was performed at diagnosis, every 6 months in the first 2 years then once yearly during follow-up or whenever necessary. Bcr-Abl kinase domain mutations were performed by allele specific oligonucleotide primers polymerase chain reaction (ASO PCR) for patients with primary resistance or suboptimal response.

For the allogeneic transplant group, different conditioning regimens were used, 117 patients received fractionated total body irradiation 250 cGy for 4 days (D-7 to D-4) and cyclophosphamide 60 mg/kg for 2 days (D-3 and D-2), (TBI/Cy protocol) during the period between May 1997 to March 2003, 71 patients received busulphan 4 mg/kg for 4 days (D-7 to D-4) and cyclophosphamide 60 mg/kg/day for 2 days (D-3 and D-2), (classical Bu / Cy) during the period between September 1998 to November 2005, 18 patients received reduced intensity regimen as fludarabine 30 mg/m2 for 3 days (D-4 to D-2) and total body irradiation 200 cGy (D-1), (Flu /TBI protocol) during the period between February 2001 to March 2003, 47 patients received spaced and fractionated Bu / Cy protocol as busulphan 4 mg/kg/day for 4 days (D-11 to D-8) and cyclophosphamide 30 mg/kg/day for 4 days (D-5 to D-2) during the period between August 2005 to April 2007, , and 34 patients received fludarabine 30 mg/m2 for 5 days (D-10,9 and D-4,3,2) and busulphan 4 mg/ m2 for 4 days (D-8 to D-5) , (Flu / Bu protocol) during the period between August 2006 to November 2008.

Results

TBI / Cy group
117 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between May 1997 and March 2003. Their median age was 29 (range 8-48 y), 62 patients (52 %) were in the first year of diagnosis at onset of transplant .
AGVHD (Grade II-IV) occurred in 43 patients (36%). Limited cGVHD occurred in 20 patients (17%) while extensive cGVHD occurred in 23 patients (19%). After a median follow-up of 9 years and 5 months (113 months) , DFS and OS were 30% and 34 % respectively. (Fig. 1)

Classic Bu / Cy group
71 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between September 1998 and November 2005. Their median age was 29 (range 3-47 y), 30 patients (42 %) were in the first year of diagnosis at onset of transplant .
AGVHD (Grade II-IV) occurred in 20 patients (28%). Limited cGVHD occurred in 3 patients (4%) while extensive cGVHD occurred in 12 patients (17%). After a median follow-up of 4 years and 5 months (53 months) , DFS and OS were 31 %. (Fig. 2)

Reduced – intensity group

18 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between February 2001 and March 2003. Their median age was 32 (range 13-49 y).None of the patients developed AGVHD. Limited cGVHD occurred in 2 patients (11%) while extensive cGVHD occurred in 12 patients (17%). After a median follow-up of 7 years and 6 months (90 months) , DFS and OS were 25 % and 50 % respectively. (Fig. 3)

Bu / Cy (spaced and fractionated) group

47 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between August 2005 and April 2007. Their median age was 28 (range 6-45 y), 18 patients (39 %) were in the first year of diagnosis at onset of transplant .

AGVHD (Grade II-IV) occurred in 10 patients (21%). Limited cGVHD occurred in 7 patients (15%) while extensive cGVHD occurred in 8 patients (17%). After a median follow-up of 3 years (36 months) , DFS and OS were 58 %. However when we stratified our patients according to onset from diagnosis until transplant, patients with less than one year had a superior outcome with a DFS and OS of 66 % compared to only 53% for patients with more than one year of diagnosis (P = 0.2). (Fig.4)

Flu / Bu group

34 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between August 2006 and November 2008. Their median age was 29 (range 18-47 y), 13 patients only (38 %) were in the first year of diagnosis at onset of transplant .

AGVHD (Grade II-IV) occurred in 8 patients (23%). Limited cGVHD occurred in 2 patients (5%) , extensive cGVHD occurred in 2 patients (5%). After a median follow-up of 2 years (24 months) , DFS and OS were 70 %. However when our patients were stratified according to onset from diagnosis until transplant, patients with less than one year had a superior outcome with a DFS and OS of 76 % compared to only 66% for patients with more than one year of diagnosis (P=0.4). (Fig. 5)

Frontline imatinib group

91 chronic phase CML patients treated with a daily oral dose of IM 400 mg during the period between March 2004 and January 2008 were evaluated after a median follow up period of 21 months (range 4-60 months) .

At 12 months of therapy 68/91(74%) patients achieved a major cytogenetic response (MCR) from whom 53 patients (53/91, 58%) were in complete cytogenetic response (CCR). At 18 months, 85 patients were evaluated for molecular responses. Fifty one patient (51/85, 60%) achieved a major molecular response (MMR); 38 patients (45%) at 12 months in addition to 13 patients (15%) at 18 months. Bcr-Abl transcripts become undetectable in 22/85 patients (26%) at 24 months follow-up on consecutive measurements. Primary resistance was observed in 16/91 (17%) patients. A suboptimal response was observed in 18/91 patients (18%). All patients with primary resistance (16/16, 100%) and 16/18 (89%) of suboptimal responders failed to achieve 2 log reductions at 6 months versus 3/57 (5%) only in the optimal responder group (p<0.0001). Bcr-Abl kinase domain mutations were performed by allele specific oligonucleotide primers polymerase chain reaction (ASO PCR) in 15 patients (10 suboptimal responders and 5 primary resistance) and was positive in 9/15 (60%) patients. **M351T** was positive in 4/15 patients (27%) and **Q252** was positive in 3 patients (20%). **F359V** and **Y253F** were positive in one patient each. **T315I** was negative in all 15 patients tested. Five patients developed acute blastic crisis (ABC) during treatment (5/91, 5%) with rising Bcr-Abl/Abl ratios (Fig. 6). All failed to achieve 2 log reductions at 6 months of IM therapy. Three tested patients out of five ABC were positive for p loop mutations (two patients Q252H and one Y253F) 5.

Cost considerations

The discovery of imatinib has changed the therapeutic algorithm for CML and is now the therapy of choice for newly diagnosed patients with marked impact on the use of allogeneic SCT in CML. In developing countries the impact has not been so marked, probably because of the cost of TKI. Median cost of each allograft was US$15000, an amount that is enough to cover 6 months of treatment with imatinib (400 mg/day). So, as most of our patient can not afford continuing treatment with TKI especially in view of the lack of a third party payer, allografting still has a relevant role when resources are limited .

Summary and conclusions

Treatment modality for CML patients has changed over the past decade from the standard allogeneic SCT as the only proven curative potential to the use of TKIs , mainly imatinib as frontline treatment. However cost considerations especially in developing countries favor allogeneic transplant as a «once only» procedure compared to a lifelong treatment with an expensive drug that has an excessive burden on resources. Despite inferior results of early transplants, and excellent initial outcome of patients receiving imatinib , it should be noted that outcome of allogeneic transplant has also improved over years which gives a rational approach to young patients with an HLA matched sibling donor who can not afford the cost of imatinib.

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Figures

Fig 1.

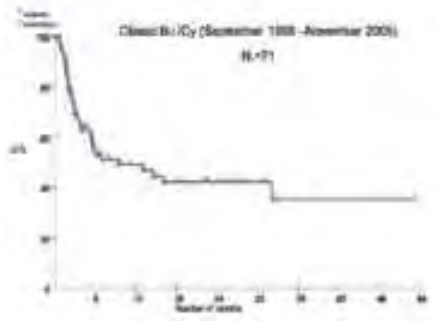

Fig 2.

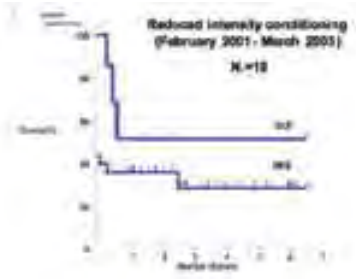

Fig 3.

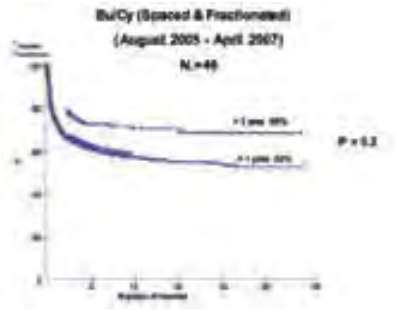

Fig 4.

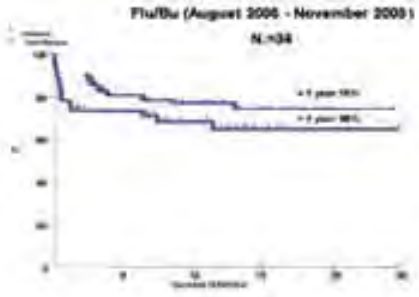

Fig 5.

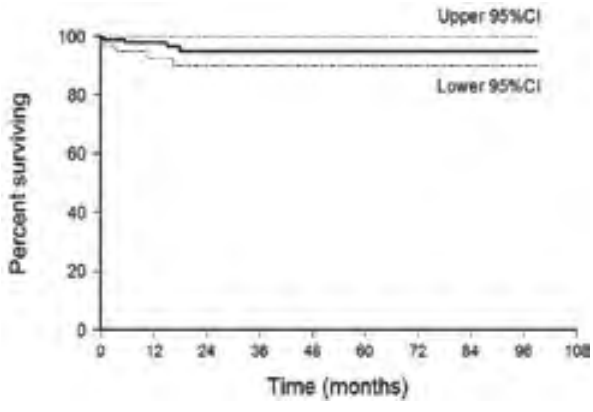

Fig 6. Frontline Imatinib group (March 2004 – January 2008) No. = 91