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CORRESPONDENCE

# Study of Haploidentical Stem Cell Transplantation for Philadelphia/BCR-ABL Positive Acute Lymphoblstic Leukemia

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Dear Editor,

Philadelphia chromosomal (Ph+) abnormality is seen in 25% of adult and 3–5% of pediatric acute lymphoblastic leukemia (ALL) patients and is associated with high relapse rates [1]. Consolidation with HLA matched or Haplo-idential Allogeneic Stem Cell Transplantation (HaSCT) has been associated with better outcome in adult Ph + ALL patients [2, 3].

We are presenting our experience of HaSCT (HLAs matched at 5–8/10 of sibling or parents) for Ph + ALL patients from January-2012 to December-2017. Patients were followed up till 30-September-2018.

Out of 58 Ph + ALL patients during study period 10 patients (males = 6, median age 27.5 years, 17–42 years) received HaSCT after achieving first or second complete remission following intensive chemotherapy and tyrosine kinase inhibitor (Imatinib = 1, Dasatinib = 9). Six patients had Philadelphia chromosome while all patients had BCR-ABL detected by PCR. At the time of HaSCT, 5 patients were in CR1 and remaining in CR2. Eight patients had BCR-ABL $< 0.1\%$.

Patients received varied intensity conditioning regimen but uniform GvHD prophylaxis with post-transplant high dose cyclophosphamide, tacrolimus and mycophenolate mofetil (see donor and transplant characteristics and outcome data in Table 1).

Acute (grade II–IV) and limited chronic GvHDs were observed in 4 and 3 patients respectively. Three patients required 2nd line agent for steroid refractory acute GvHD with complete resolution and survival in all. CMV reactivation (Cut off limit for CMV infection was 500 copies/ml) was observed in 9/10 (90%) with 1 patient dying of CMV pneumonia at day + 30.

Major events were non-relapse mortality (NRM) (n = 2, CMV pneumonia and bacterial infection), relapse (n = 2) and graft rejection (n = 1). Overall 4 patients died (NRM = 2, progressive disease = 2), all from CR2 cohort.

PFS is defined as time from transplant till progression of disease, non relapse mortality (NRM) or last follow-up.

EFS is defined as time from transplant till progression of disease, graft rejection, NRM or last follow-up.

At a median follow up of 27 (13–37) months, estimated 2 year OS, EFS and PFS were 60% ± 15%, 50% ± 16% and 60% ± 15% respectively. One year estimated OS and PFS for patients transplanted in CR1 versus CR2 were 100% ± 0% versus 20% ± 18% ($p = 0.01$, log rank) and 100% ± 0% versus 20% ± 18%; ($p = 0.01$, log rank) respectively.

Chen et al. [2] reported better OS for patients transplanted in CR-1 versus CR-2 (HR 2.7, $p = 0.023$). Santoro et al. [4] showed better OS of CR1 (52%) transplanted patients than CR2 (34%) and patients with advanced disease (4%) ($p < 0.01$). Srour et al. [5] showed improved disease free survival at 3 year of CR1 (52%) and CR2 (30%) transplanted patients ($p = 0.082$).

Gao et al. [3] reported a higher incidence of aGvHD (51% vs. 25.7%) and CMV infection (38.3% vs. 14.3%) in HaSCT versus HLA matched transplants. Our cohort had very high rates of CMV infection which may be due to high CMV positivity amongst recipients and donor (Table 1).

In conclusion, HaSCT, if performed in CR-1, achieves promising survival rate for Ph + ALL patients. CMV infection rates were very high and warrant a HaSCT

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**Table 1** Baseline demographics, donor and transplant characteristics and outcome

| Variables | N | Median |
|---|---|---|
| *Baseline patient and disease characters* | | |
| Age | | 27.5 years (17–42 years) |
| Males | 06 | |
| Females | 04 | |
| Bone marrow cytogenetics | | |
| Philadelphia chromosome | 06 | – |
| Additional cytogenetics abnormalities | 04 | |
| Normal karyotype | 01 | |
| Not available | 03 | |
| BCR-ABL transcript | | |
| P190 | 08 | – |
| P210 | 02 | |
| CNS-1 | 10 | – |
| Pre-transplant remission status | | |
| CR-1 | 05 | – |
| CR-2 | 05 | |
| Pre-transplant BCR-ABL | | – |
| $< 0.1\%$ | 08 | |
| $> 0.1\%$ | 02 | |
| *Transplant characteristics* | | |
| Donor | | |
| Age | – | 41.5 years (19–60 years) |
| Male:female | 06:04 | |
| Parents as donor | 04 | |
| Siblings as donor | 06 | |
| Female to male transplant | 04 | |
| Male to female transplant | 03 | |
| CMV seropositive recipient | 09 (90%) | – |
| Source of stem cell | | – |
| Peripheral Blood | 10 (100%) | |
| Conditioning regimen | | – |
| Reduced Intensity Conditioning (RIC) | 07 | |
| (Fludarabine 150 mg/m$^2$–Cyclophosphamide 29 mg/kg–TBI 200 cGy) | | |
| Myeloablative | 03 | |
| (Fludarabine 90 mg/m$^2$–TBI 800 cGy) | 01 | |
| (Busulfan 360 mg/m$^2$–Fludarabine 125 mg/m$^2$–Cyclophosphamide 29 mg/kg) | 02 | |
| Stem cell dose | – | $5 \times 10^6$/kg ($3.85–6.2 \times 10^6$/kg) |
| Neutrophil engraftment | – | + 16 day (+ 7 to + 26 day) |
| Platelet engraftment | – | + 20 day (0 to + 31 day) |
| CMV reactivation | 09 | + 32 day (+ 17 to + 47 days) |
| CMV disease | 01 | + 30 day |
| aGvHD | 04 | + 26 day (+ 21 to + 115 day) |
| cGvHD | 03 | + 223 day (+ 179 to + 379 day) |
| Events | | |
| Graft rejection | 01 | + 25 day |
| Non-relapse mortality | 02 | Day + 30 and + 57 |
| Relapse | 02 | Day + 124 and + 207 |

**Table 1** continued

| Variables | N | Median |
|---|---|---|
| Overall mortality | 04 (40%) | – |
| Progressive disease related mortality | 02 | |
| Non-relapse mortality | 02 | |
| *Outcome* | | |
| Survival, Median follow up | 06 | 27 months (13–37 months) |
| 2 years, estimated PFS and OS | – | 60% ± 15% |
| 2 years, estimated EFS | – | 50% ± 16% |
| PFS and OS at 1 year follow-up | | $p = 0.01$ |
| CR-1 | 100% ± 0% | |
| CR-2 | 20% ± 18% | |
| EFS at 1 year follow-up | | $p = 0.10$ |
| CR-1 | 80% ± 18% | |
| CR-2 | 20% ± 18% | |

specific CMV prophylactic strategy. Our study has limitations of being a retrospective study of a small cohort and short follow up.

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**Compliance with Ethical Standards**

**Conflict of interest** Narendra Agrawal, Neha Yadav, Priyanka Verma, Priyanka Soni, Pallavi Mehta, Shinto Francis Thekkudan, Rayaz Ahmed, Dinesh Bhurani declare that they have no conflict of interest.

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