Stem cell transplantation in the TKI era

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April 23, 2010
The beginning of SCT in CML

- CML pts given intensive chemo/radiotherapy and bone marrow from their syngeneic twin donors led to the disappearance of the Ph chromosome marked the beginning of a new era in the treatment of CML.

Fefer, Buckner and Thomas
N Engl J Med 1977;297:146-8
The concept was rapidly adopted and followed by SCT from HLA identical sibling donors.

The efficacy of allogeneic SCT was proven in several large series in Europe and USA.

Allogeneic SCT became the standard treatment for patients with CML and compatible donor.

At the end of the last decade, CML was the most frequent indication for an allogeneic transplant worldwide.

More than 1000 SCT were reported to EBMT activity survey in 1999.
The introduction of the specific tyrosine kinase inhibitor (TKI) imatinib changed this trend completely.

As early as in the year 2000, the numbers of HSCT for CML began to decline, years before the results of the first clinical trials with imatinib were published.

The numbers of HSCTs in advanced stages of the disease remained relatively stable.

There is no prospective study comparing SCT to imatinib.

Several publications compared the results obtained with imatinib to historical controls.
Fig. 1. Numbers of allogeneic and autologous HSCT for CML reported to the EBMT activity survey from 1990 to 2007.
Transplant rates (number of transplantations per 10 million inhabitants) for CML in Europe from 1990 to 2004 by world bank category for Gross National Income per capita (www.worldbank.org).
Recruitment: Jan 1995-Dec 2001

Hehlmann, et al

Figure 1. Flow diagram of enrollment, allocation, follow-up, and analysis of patients.
Figure 3. Survival of all 354 Ph- or BCR-ABL-positive CML patients that were eligible for transplantation and genetically randomized according to availability of a related donor. The survival times of patients who received an unrelated transplant in first chronic phase were censored at the day of transplantation. The survival differences were significant for the entire period and for the time until the curves converge (first cut point, year 8) (Wilcoxon-Gehan test: $P = .049$ and $P = .041$, respectively). For patients at risk see Table 2. m.s. indicates median survival. The error bars signify 95% confidence intervals.
Low risk
High risk
On the basis of up to 11 years follow-up, the general recommendation of SCT for all pts as first line treatment in CP,CML can no longer be maintained.

Hehlmann, et al
Retrospective analysis of 264 pts in CML, CP in Brazil (2001-2006)

<table>
<thead>
<tr>
<th></th>
<th>HSCT</th>
<th>Imatinib after IFN failure</th>
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<tr>
<td><strong>n</strong></td>
<td>90</td>
<td>174</td>
</tr>
<tr>
<td>Med. Time from dx to tx</td>
<td>16(5-104)</td>
<td>19(2-205)</td>
</tr>
<tr>
<td>5y EFS</td>
<td>51.8%</td>
<td>79.3% *IFN intolerant</td>
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<td></td>
<td></td>
<td>52.6% IFN resist</td>
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<tr>
<td>5y OS</td>
<td>58.8%</td>
<td>92.7%*</td>
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Bittencourt, et al
BMT 2008, 42:597-600
**Figure 1** EFS IM versus allo-BMT group (n = 264).
Bittencourt, et al
BMT 2008, 42:597-600
Influence of pre-treatment on outcome after HSCT

- Early studies clearly showed a detrimental effect of busulphan on TRM.

- Interferon alpha has no detrimental effect if withheld during 3 months before SCT.

- No indication that treatment with TKIs increases the risk of organ toxicity or other post-transplant complications.
Stem cell source

- PBSCT has become the preferred source of stem cells for allogeneic transplants
- PBSC is associated with a significantly more rapid neutrophil and platelet engraftment
- PBSCT is also associated with a significantly higher incidence and severity of acute and chronic GVHD
- The best stem cell source is therefore still a matter of debate as well as the role of RIC HSCT.
- Survival was primarily influenced by the EBMT risk score
HCT for CML: Main risk factors

**Table 3. AlloHSCT Risk Factors and EBMT Risk Score**

<table>
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<tr>
<th>Risk Factor</th>
<th>Score and Description</th>
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<tr>
<td>Disease phase</td>
<td>0 if CP; 1 if AP; 2 if BP</td>
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<tr>
<td>Age</td>
<td>0 if &lt; 20 years; 1 if 20-40 years; 2 if &gt; 40 years</td>
</tr>
<tr>
<td>Interval from diagnosis</td>
<td>0 if ( \leq 1 ) year; 1 if &gt; 1 year</td>
</tr>
<tr>
<td>Donor type</td>
<td>0 if HLA-identical sibling; 1 in any other instance</td>
</tr>
<tr>
<td>Donor-recipient sex match</td>
<td>1 if female donor and male recipient; 0 for any other match</td>
</tr>
</tbody>
</table>

SCT in Ramathibodi Hospital during 1998-2007

- Total patients: 36
- Median age: 33 (16-49)
- M: F 24: 12
- CP 80%
- EBMT score low: intermediate: high 30.6: 58.3: 11.1
Overall survival of 36 CML patients undergoing SCT in Ramathibodi Hospital during 1998-2007

10 y-OS = 52%
Points to consider for developing countries

- Drug treatment with TKI is superior to allografting as first line therapy for CML.

- In developing countries it is cheaper to perform an allo SCT as “once only” procedure than to offer the patient a life time treatment with TKI.
Cost-Efficacy of Imatinib versus Allogeneic Bone Marrow Transplantation with a Matched Unrelated Donor in the Treatment of Chronic Myelogenous Leukemia: A Decision-Analytic Approach

Imatinib was both less costly and more efficacious than BMT in the 2-year treatment of CML

Skrepnek GH, Ballard EE
(Pharmacotherapy 2005;25(3):325–334)
Patients in first chronic phase

- Allo SCT is recommended in all patients who failed second line TKI
- Allo SCT is recommended for all patients in case of accelerated phase, blastic transformation and T315I mutation
- Allo SCT is a significant option in patients who have suboptimal response to dasatinib or nilotinib as the second line.
- It is recommended if this patient had prior hematologic resistance to imatinib, has developed mutations or has a low EBMT risk score
Patients in advanced disease

- Treatment recommendations are substantial for the patients who are referred in accelerated or blastic crisis.
- All these patients should be submitted to allogeneic SCT.
- If eligible, they should be pretreated with high dose imatinib if they were TKI naive, with dasatinib or nilotinib if they were imatinib resistant.
- Other agents should be chosen if they carry the T315I mutation.
- The commitment to allo SCT in these patients is supported by the observation that the duration of response is short even if the TKI can be very effective.
Conclusion 1

- Allo SCT should be considered as a first-line therapy for pts with advanced disease, accelerated phase or blastic crisis, after pre-treatment with TKIs.
- Allo SCT should be considered second-line therapy for pts who failed imatinib and a low risk for SCT, for pts with progression to advanced phase during TKI treatment.
- Allo SCT should be considered third-line therapy for all pts who failed second-line TKIs.
- A donor search should always be initiated at time of diagnosis for pts with advanced disease and at time of imatinib failure for all others.
- In situation with limited resources allo SCT might be the most cost-efficient approach.
 Allo SCT for patients with CML remains an important treatment option.

 Indication for an allo SCT depends on the risk of the disease, the response to the first line therapy, and the risk of the transplantation.

 Risk factors for outcome after SCT are clearly defined: age of pts, stage of the disease, time from diagnosis to transplantation, HLA compatibility and donor-recipient sex combination.
Thank you for your attention

Have a great weekend