Clinical Area: Autologous SCT/BMT for CML.

Keywords: Chronic myeloid leukemia, autologous bone marrow transplantation, autologous peripheral blood stem cell transplantation.


Study Type: Case Series.
Study Aim: To report the results of the effect of autologous transplants for CML patients in eight bone-marrow-transplant groups.

Outcomes
Primary: Patient survival, activity level.

Design:
- Number of subjects: N=200 patients from eight transplant centers.
- Method of subject selection (inclusion/exclusion criteria): Philadelphia chromosome (Ph) positive patients with CML receiving autologous transplants.
- Consecutive patients? Patients were consecutive in each of the eight marrow-transplant groups.
- Description of study population: These were patients who received autologous transplants in eight marrow transplant centers in the United States, Canada, and Europe, from June 1984 to January 1992. Their ages ranged from 7 to 67 years, with a median of 42 years. All the patients were Ph positive. 142 (71%) were in the chronic phase at time of the transplant, 30 (15%) were in the accelerated phase, and 28 (14%) were either in the blast crisis phase or in a stable phase after a blast crisis. The median interval from diagnosis to the transplant was 14.6 months (range 2-113 months).
- Exposure/Intervention: All patients received an autologous transplant. 127 (63.5%) received bone marrow and 73 (36.5%) received peripheral blood as a source of autologous stem cells.
- Source of outcome data (e.g. patient self-report, doctor report, lab results): Clinical evaluation to assess activity and well being following transplant, and survival data.
- Length of follow-up: 1-91 months with a median of 30 months.
- Completeness of follow-up: Data were obtained for all patients included in the analysis, but with a variable follow-up period which was a short as one month for some patients.

Validity:
- Is the study type appropriate for the question(s) being asked? No, a randomized controlled study would be more appropriate.
- Were patients similar with respect to baseline characteristics? No, it was a heterogeneous group of patients.
- Were the intervention and other aspects of patient care similar for all patients (or for all patients in a defined subgroup)? Basically all patients received either a marrow or peripheral blood autologous transplant. Not all cells received the same treatment prior to the transplant. In one center the marrow cells were cultured ex-vivo prior to infusion, and in another center the marrow was incubated in-vitro with recombinant human interferon gamma prior to infusion.
- Was the process of observation likely to affect the outcome? Probably not.
- Did an objective observer assess outcomes and were outcome measurements consistent? Not discussed.
- Was follow-up duration appropriate? No, this was as short as one month for some patients.
- Was follow-up rate sufficient? Not discussed.

Conclusions regarding validity of methods:
This study was an analysis of data pooled from eight marrow transplant centers. It is subject to the same internal validity threats of all case series including selection bias, observation bias, non-blinding, lack of a control or comparison group, confounding, and other threats. Moreover, this study combined patients from eight centers, which may have had different protocols and different eligibility criteria.
Results:

Survival:

Median survival time post transplant = 42 months.

<table>
<thead>
<tr>
<th>Survival experience according to stage of CML at transplantation</th>
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<tbody>
<tr>
<td>CML Phase at transplantation</td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>First chronic phase (CP)</td>
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<tr>
<td>Accelerated phase (AP)</td>
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<tr>
<td>Blast crisis phase (BC)</td>
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</tbody>
</table>

* p<0.0001 between the three stages  ** Some patients were still alive at the seven years of follow-up.

Effect of age on survival of patients in the chronic phase:
Short-term survival* was significantly better for patients ≤ 40 years of age vs. patients older than 40 years (p<0.01).
Long term survival* was also better for patients ≤ 40 years, but the difference was not statistically significant (p=0.07).

*Short and long term survivals were not defined but it appears to be < or > 3 years respectively.

Activity level* after the transplant:
Normal activity (Karnofsky score =100%): 73% of the patients.
Mild to moderate activity impairment (Karnofsky score 80-90%): 21% of the patients.
Significant debility (Karnofsky score ≤ 70%): 6% of the patients.

* According to Karnofsky score.

Authors’ Conclusions:
The authors concluded that autografting may be an alternative treatment to conventional therapies for patients not eligible for donor transplant.

Reviewer’s Conclusions:
This multicenter analysis of autologous transplant shows that there was a plateau of survival from 3.6 to 7.5 years for patients in the first chronic phase of CML. These patients had a significantly higher survival than those in the accelerated phase, or the blast phase, who had the lowest survival. This is generally expected, when the life expectancy is shorter for patients in the advanced stages. The results of this study should be interpreted cautiously due to nature of the study design, potential selection and observation biases, and lack of control or comparison groups.