Symposium article

Stem-cell transplantation for chronic lymphocytic leukemia: The 1999 perspective

P. Dreger,¹ M. Michallet² & N. Schmitz¹
¹Second Department of Medicine, University of Kiel, Germany; ²Unité de Greffe de Cellules Souches Hématoopoïétiques, Hôpital Edouard Herriot, Lyon, France

Summary

Background: The use of myeloablative intensive therapy followed by autologous or allogeneic stem-cell transplantation (SCT) for treatment of chronic lymphocytic leukemia (CLL) has largely increased over the last years.

Design: The present overview updates the available clinical results and discusses important aspects of SCT in patients with CLL including the type of SCT (autologous vs. allogeneic), myeloablative regimens, purging, the predictive value of molecular monitoring of residual disease, and prognostic factors for the outcome of transplant approaches.

Results: With appropriate supportive care, autologous SCT is safe and can induce long-lasting clinical and molecular remissions, which may improve the prognosis of patients with CLL. Feasibility and efficacy of autologous SCT appears to be best early during the course of the disease, but it is still unclear if autotransplantation can cure the disease even in this favorable subgroup. The role of purging is still unclear. The better disease control observed after allografting appears to be due to graft-versus-leukemia activity and may allow cure in at least a subset of poor-risk patients. Due to the extraordinarily high treatment-related mortality, however, the outcome after allogeneic SCT is still inferior to that after autologous SCT.

Conclusions: Autologous transplantation is a valuable treatment option for younger patients with early or sensitive poor-risk CLL. Selected patients with advanced poor-risk disease and low probability of successful auto-SCT should be considered for allografting. However, it must be kept in mind that both autologous and allogeneic stem-cell transplantation are still experimental procedures and clinical trials further elucidating their value in the treatment of patients with CLL are warranted.

Key words: CLL, therapy, stem-cell transplantation, prognosis

Introduction

A few years ago, we have discussed some key issues in the context of stem-cell transplantation (SCT) for chronic lymphocytic leukemia (CLL) [1]. Meanwhile, the interest and the clinical activities in this particular field have dramatically increased, as illustrated by the fact that more than 50% of all transplants ever reported to the European Blood and Marrow Transplant (EBMT) registry have been performed during the past three years. The purpose of this article is to reexamine the mentioned crucial issues of SCT for CLL in the light of the additional information that has become available over this period of time. Topics which will be addressed include the type of SCT (autologous vs. allogeneic), myeloablative regimens, stem-cell source, purging, the predictive value of molecular monitoring of residual disease, and prognostic factors for the outcome of transplant approaches.

Results of allogeneic stem-cell transplantation

Although CLL is one of the most common hematological neoplasms, it is still a rare indication for allotransplantation. This certainly has to do with the fact that many patients with CLL are older and/or have indolent disease which does not justify aggressive treatment. Another important reason, however, is the high toxicity associated with allografting for this particular indication. Even in well-experienced centers, the treatment-related mortality (TRM) of allogeneic SCT in patients with CLL is reported to be as high as 36% (Table 1). This figure further increases if registry data are taken into account: A recent update of the EBMT database comprising 188 allografted patients with CLL disclosed a TRM of 49% at 36 months post transplant, which is clearly more than after standard indications such as acute leukemias or chronic myeloid leukemia (CML) [2-4]. The causes of these discouraging results are not completely clear, but patient age, selection of poor risk patients with advanced disease and extensive pretreatment, and the CLL-associated incompetence of the immune system may all contribute to the high TRM observed. The recent development of conditioning regimens with reduced intensity may help to improve the tolerability of allo-SCT in patients with CLL [5, 6].

On the other hand, relatively few relapses occur after allogeneic transplantation (15% within the first three years in the EBMT series) [2, 3], and the survival curves
appear to approach a plateau in the long term, suggesting that allotransplantation may have curative potential in this disease [7, 8]. Accordingly, in the three larger US trials as well as in the EBMT database the overall survival is reported to be 45% to 60% at three to four years post transplant (Table 1).

**Results of autologous stem-cell transplantation**

In contrast to allogeneic transplantation, autografting of patients with CLL has dramatically increased over the past years and is now the preferred type of transplant with 225 cases in the EBMT database and a growing number of published single-center series [3, 9-14]. Due to the event of mobilized peripheral blood stem cells and other improvements of supportive therapy, the mortality of the procedure could be further reduced and should be clearly below 10% in 1999. High-dose radiochemotherapy followed by autologous SCT can induce or maintain long-term complete remissions. Nevertheless, in most series a steady decline of the event-free survival curve is observed due to continuous relapses occurring up to five years post transplant, and it is still not clear if autografting can be curative in at least certain subsets of patients with CLL. Probably depending on patient selection and perhaps also on technical details such as stem-cell source and purging, the frequency of relapses strongly varies between different series (Table 2). Due to the low toxicity of the procedure, the outcome of autografted patients is characterized by three-year overall survival figures of more than 75% and, thus, is generally superior to that after allotransplantation.

**Allogeneic or autologous stem-cell transplantation?**

It becomes increasingly clear that allogeneic and autologous transplantation are fundamentally different treatment approaches in particular in the context of indolent diseases such as CLL. Whereas efficacy (and complications) of autografting rely exclusively on the cytotoxic therapy administered, the crucial anti-leukemic principle of allotransplantation appears to be the immune-mediated anti-host activities conferred with the graft [GVL (graft versus leukemia) effect] [6]. Accordingly, autologous SCT adds nothing else than intensity (and perhaps a radiotherapeutic component) to conventional treatment. For this reason, the toxicity of autotransplantation is nowadays only slightly higher than that of intensive conventional chemotherapeutic regimens, but its capacity for complete eradication of resistant CLL clones seems to be limited, too. On the other hand, allogeneic transplantation introduces the entirely different modality of cellular immune therapy, which appears to be responsible for its superior anti-leukemic activity as well as for its considerably higher toxicity.

Apart from the basic considerations listed in Table 3 we therefore believe that autologous transplantation is preferable for patients with early or sensitive disease (see also below). Selected patients with advanced poor-risk disease and low probability of successful auto-SCT as suggested below should be considered for allografting. However, it must be kept in mind that both autologous and allogeneic stem-cell transplantation are still experimental procedures which should not be performed outside of approved clinical trials.

**Myeloablative regimens**

Although encouraging results have been observed after high-dose chemotherapy alone followed by autologous SCT [14], in the vast majority of published stem-cell transplants for CLL the myeloablative regimen contained total body irradiation (TBI). The rationale behind this is that CLL cells – similar to other indolent lymphoid neoplasms – are sensitive to irradiation. On the other side, it is unlikely from the results of conventional therapy that cytotoxic drugs alone can eradicate CLL. Since in the allogeneic setting the GVL activity can be the crucial effector of disease eradication, the direct anti-leukemic effects of the conditioning regimen may not be as important as initially believed. Provided that

### Table 1. Allogeneic SCT in CLL

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Age</td>
<td>43 (25-55)</td>
<td>44 (28-54)</td>
<td>46 (28-60)</td>
</tr>
<tr>
<td>Maximum Binet stage</td>
<td>B-C</td>
<td>B-C</td>
<td>C</td>
</tr>
<tr>
<td>TRM</td>
<td>27%</td>
<td>22%</td>
<td>36%</td>
</tr>
<tr>
<td>Relapse</td>
<td>20%</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>Disease-free survival (four-year)</td>
<td>53%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Overall survival (four-year)</td>
<td>57%</td>
<td>50%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>35 (3-60)</td>
<td>30</td>
<td>23 (9-103)</td>
</tr>
</tbody>
</table>

### Table 2. Autologous SCT in CLL

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>81</td>
<td>16</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Maximum stage</td>
<td>B-C</td>
<td>B-C</td>
<td>A-C</td>
<td>B-C</td>
</tr>
<tr>
<td>SC source</td>
<td>BM</td>
<td>BM 3: unoblized PB 13 no</td>
<td>BM: mobilized PB 35 no</td>
<td>PB</td>
</tr>
<tr>
<td>Purging</td>
<td>B-CD, PB 35 no</td>
<td>TBI/CY; BEAC</td>
<td>TBI/CY</td>
<td>BEAM</td>
</tr>
<tr>
<td>HD regimen</td>
<td>TBI/CY</td>
<td>TBI/CY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRM</td>
<td>10%</td>
<td>19%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Relapse</td>
<td>17%</td>
<td>56%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Disease-free survival (four-year)</td>
<td>63%</td>
<td>28%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Overall survival (four-year)</td>
<td>8%</td>
<td>58%</td>
<td>95%</td>
<td>85%*</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>30</td>
<td>41 (22-125)</td>
<td>14 (3-67)</td>
<td>18</td>
</tr>
</tbody>
</table>

* Two-year overall survival
they are immunosuppressive enough to establish a donor chimerism, a variety of preparative treatments may be therefore suitable in this situation [5, 6].

Thus, TBI/cyclophosphamide appears to be still the gold standard for autografting of patients with CLL, whereas in the context of allotransplantation reduced intensity conditioning promises to be an elegant tool for conferring powerful GVL activities while avoiding the toxicity of cytotoxic myeloablation.

### Stem-cell source

Due to their favorable engraftment kinetics, mobilized PBSC have replaced now bone marrow as the principal source of stem cells for autotransplantation [4]. In the particular situation of CLL, PBSC have the additional advantage of maintaining their hematopoietic potential in spite of vigorous ex vivo manipulation for purposes of purging. Thus, mobilized PBSC are the stem-cell source of choice in the autologous setting. A variety of G-CSF-based mobilization regimens is currently in use. As suggested by the results summarized in Table 4, the mobilization efficacy of more intensive protocols, such as the Dexa-BEAM regimen, appears to be somewhat better than that of classical cyclophosphamide plus G-CSF combinations [9, 13-15]. Other variables that may influence mobilization efficacy are the extent of chemotherapeutic pretreatment and previous exposition to fludarabine [16].

Similarly, in the allogeneic setting PBSC seem to have some advantages over marrow grafts in terms of engraftment kinetics and hematopoietic capacity which might be especially important in the context of intensity-reduced conditioning. However, also bone marrow can be successfully used in this situation.

### Purging

The performance of systems for ex vivo B-cell depletion from stem-cell grafts has been further refined during the recent years. With modern CD34+ selection devices, such as Isolex300i or Clinimacs, it is possible to eliminate three to four log of CLL cells from fresh leukapheresis products [17]. The purging efficacy can be further increased up to six log by incorporating a step of negative B-cell depletion into the procedure [18]. This maneuver allows also the elimination of presumptive CD34+ CLL cells. In spite of sophisticated purging technologies, only little additional information on the clinical benefit of ex vivo B-cell depletion has been gained, meaning that clear-cut evidence for the usefulness of purging of CLL autografts is still lacking [3]. As long as cure is intended, however, we believe that autotransplantation concepts in patients with CLL should comprise effective purging of PBSC to rule out the possibility that successful disease eradication in vivo is counteracted by reinfusion of tumor cells along with the graft.

### Molecular monitoring

Because complete eradication of CLL is impossible to assess by clinical criteria alone, adequate monitoring of minimal residual disease requires sensitive tumor-specific markers. To date, molecular-genetic assessment of the clonal CDR3 rearrangement of the IgH gene by PCR-amplification using clone-specific primers seems to be the best method available in terms of sensitivity and specificity. With this strategy, we and others have shown that persistence of the tumor-specific PCR signal after autografting is strongly predictive for subsequent disease recurrence, whereas patients achieving molecular remission are not at risk for short-term relapse [19-21]. Thus, molecular monitoring with clone-specific CDR3 probes allows an early view at the extent of in vivo leukemia eradication and may be useful for evaluating the therapeutic potential of transplantation.

### Factors predictive for the outcome of autologous SCT

In our 1997 review we speculated that a short interval from diagnosis to transplant and a status of minimal

---

**Table 3. Advantages and disadvantages of autologous vs. allogeneic SCT.**

<table>
<thead>
<tr>
<th></th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>No need for a donor</td>
<td>Tumor cell contamination of the graft</td>
</tr>
<tr>
<td>SCT</td>
<td>Low mortality, no GVHD</td>
<td>No GVL effects</td>
</tr>
<tr>
<td></td>
<td>Superior survival in comparison to allogeneic SCT</td>
<td>No plateau in survival curve</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>No need for purging</td>
<td>Needs donor</td>
</tr>
<tr>
<td>SCT</td>
<td>GVL activity; possibility of donor lymphocyte infusion</td>
<td>High mortality with standard conditioning</td>
</tr>
<tr>
<td></td>
<td>Probably plateau in survival curve</td>
<td>Survival still inferior to autologous SCT</td>
</tr>
</tbody>
</table>

**Table 4. Mobilization strategies for autologous SCT in CLL.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>No. of previous chemotherapy regimens</td>
<td>0</td>
<td>0 (0–3)</td>
</tr>
<tr>
<td>Cytoreduction</td>
<td>Fludarabine</td>
<td>CHOP (fludarabine)</td>
</tr>
<tr>
<td>Mobilization regimen</td>
<td>Cy 1.5 g/m² + G-CSF</td>
<td>Dexa-BEAM + G-CSF</td>
</tr>
<tr>
<td>Median CD34+ cell yield (x10⁹/kg)</td>
<td>2.4</td>
<td>18.0</td>
</tr>
<tr>
<td>No. with mobilization failure</td>
<td>21 (23%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Engraftment (median days to)</td>
<td>Neutrophils &gt; 0.5 x 10⁹/l</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Platelets &gt; 20 x 10⁹/l</td>
<td>15</td>
</tr>
</tbody>
</table>
disease prior to transplant might be important prerequisites for the success of autografting strategies in patients with CLL [1]. Although sound evidence for these hypotheses is still lacking, some preliminary analyses of our own data support the concept of early transplant: in our cohort of 53 patients at risk, ten patients (19%) were regarded as protocol failures because they had insufficient mobilization (< 1 x 10^6/kg CD34+ cells per leukapheresis) or were not in a state of minimal disease after mobilization. Factors associated with protocol failure with were high Binet stage at mobilization (B/C vs. A; \( P = 0.017 \)), time from diagnosis to mobilization (> 12 months vs. < 12 months; \( P = 0.08 \)), and intensive chemo-therapeutic pretreatment (\( P = 0.0025 \)). In addition, the event-free survival post transplant tended to be worse in the Binet B/C patients (unpublished data). In the EBMT analysis, time from diagnosis to transplant was identified as an adverse prognostic factor in terms of overall survival (> 36 months: three-year survival 64%; < 36 months: 89%). These data indicate that autografting for CLL indeed might render best results if it is performed early during the course of the disease.

Current study activities

As mentioned earlier, the value of autologous and allo-geneic transplant approaches within established treat-ment schedules and in the context of other experimental therapies is not known. Thus, clinical studies are mandato-ry. A number of national multicenter trials aiming at the feasibility of upfront autografting in patients with poor-risk CLL are currently underway. The British Medical Research Council CLL pilot trial explores a sequential strategy consisting of initial cytoreduction with fludarabine followed by cyclophosphamide/G-CSF mobilization and high-dose radiochemotherapy with reinfusion of purged PBSC. More than 80 previously untreated patients have been recruited to this single arm study within three years. The CLL3 study launched by the German CLL Study Group has a very similar design but recommends CHOP chemotherapy for cytoreduction and PBSC mobilization with Dexa-BEAM similar to the Kiel approach. This trial is planned for 70 patients with untreated poor-risk CLL. The accrual is expected to be completed by the end of 1999. Preliminary results from both trials suggest that the respective approaches are safe and feasible in a multicenter protocol [13]. Very recently, the Italian Group for Hematological Diseases of Adults (GIMEMA) has started the first randomized trial for chemotherapy-naive patients with poor-risk CLL. This study investigates the progression-free sur-vival after four cycles of fludarabine, PBSC mobilization with cyclophosphamide plus G-CSF, and high-dose therapy with melphalan/mitoxantrone and stem-cell reinfusion in comparison to two further courses of fludarabine.

Conclusions

Autologous and allogeneic stem-cell transplantation appear to be fundamentally different treatment modalities for patients with CLL. The efficacy of autografting relies exclusively on the cytotoxic therapy administered. With appropriate supportive care, it is safe and can induce long-lasting clinical and molecular remissions. Feasibility and efficacy of autologous SCT appears to be best early during the course of the disease, but it is still unclear if autotransplantation can cure the disease even in this favorable subgroup.

The crucial anti-leukemic principle of allotransplan-tation consists in the immune-mediated GVL effects conferred with the graft. The GVL activity should be responsible for the better disease control observed after allografting which seems to be a curative treatment for at least a subset of poor-risk patients. Due to the extra-ordinarily high TRM, however, the outcome after allo-geneic SCT is still inferior to that after autologous SCT. The development of conditioning regimens with reduced intensity may help to solve this problem.

Taken together, we think that autologous transplantation is preferable for patients with early or sensitive disease. Selected patients with advanced poor-risk dis-ease and low probability of successful auto-SCT should be considered for allografting. However, it must be kept in mind that both autologous and allogeneic stem-cell transplantation are still experimental procedures and clinical trials further elucidating their value in the treat-ment of patients with CLL are warranted.

Acknowledgement

Supported by the José Carreras Leukämie-Stiftung (DJCLS 97/NAT-4).

References

7. Khouri IF, Przepiorka D, van BK et al. Allogeneic blood or
marrow transplantation for chronic lymphocytic leukaemia:  
Timing of transplantation and potential effect of fludarabine on  
transplantation from related or unrelated donors for B-CLL.  
9. Dreger P, von Neuhoff N, Kuse R et al. Early stem-cell trans- 
plantation for chronic lymphocytic leukaemia: A chance for cure?  
transplantation in chronic lymphocytic leukemia: A report of 12  
allogeneic bone marrow transplantation for patients with poor-  
after autologous stem-cell transplantation for B-cell chronic  
lymphocytic leukemia or small-lymphocytic lymphoma Ann  
13. Milligan DW, Davies FE, Morgan GJ et al. Fludarabine followed  
by stem-cell autografting for younger patients with CLL: Prelimi- 
nary results from the MRC pilot study. BMT 1999, 23 (Suppl 1):  
S53 (Abstr).
by unmanipulated PBSC: A single-center experience on 20 CLL  
15. Scime R, Indovina A, Santoro A et al PBSC mobilization,  
collection and positive selection in patients with chronic lympho- 
16. Michallet M, Apperley J. Peripheral blood progenitor cell mobi- 
 lisation and transplantation after fludarabine in chronic  
lymphocytic leukemia in Europe. BMT 1997; 19 (Suppl 1): S146  
(Abstr).
17. Dreger P, Viehmann K, von Neuhoff N et al. Autografting of  
highly purified peripheral blood progenitor cells following mye- 
loablative therapy in patients with lymphoma: A prospective  
study of the long-term effects on tumor eradication, reconstitu- 
tion of hematopoiesis and immune recovery. BMT 1999; 23 (in  
press).
18. Paulus U, Schmitz N, Viehmann K et al. Combined positive/  
negative selection for highly-effective purging of PBPC grafts:  
19. Provan D, Bartlett-Pandite L, Zwicky C et al. Eradication of  
polymerase chain reaction-detectable chronic lymphocytic leuke- 
mia cells is associated with improved outcome after bone-marrow  
20. Donnovan JW, Andersen NS, Poor CM et al. Prospective analysis  
of minimal residual disease detection in patients with CLL under- 
going autologous and allogeneic BMT. Blood 1998; 92: 652a  
(Abstr).
residual disease after stem-cell transplantation for chronic lym- 
92: 652a (Abstr).

Correspondence to:
Dr P. Dreger
Second Department of Medicine
Chemnitzstr. 33
24116 Kiel
Germany