Indications for HSCT in adults

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Chronic lymphocytic leukaemia

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1. Introduction

Both autologous and allogeneic HSCT are continuing to be explored for the treatment of chronic lymphocytic leukaemia (CLL). The annual numbers of allogeneic transplants (allo-HSCT) for CLL registered with the EBMT are steadily increasing, making this the most frequent indication for allo-HSCT among the lymphoma subtypes. In contrast, autologous transplantation numbers for CLL are steadily declining with fewer than 50 cases reported in 2009 (Figure 1).

Figure 1: Case numbers registered with the EBMT for autologous (blue) and allogeneic (yellow) stem cell transplantation between 2000 and 2009

2. Indications

2.1 Allogeneic HSCT

In CLL, allo-HSCT is a possible treatment option for patients who have poor-risk disease as defined by the EBMT CLL Transplant Consensus (Table 1) (1). Although controlled trials are lacking, available evidence strongly suggests that allo-HSCT is currently the only therapy with curative potential in CLL. In contrast to conventional treatment, including purine analogue-rituximab combination regimens, it can provide long-term disease control even in patients with an unfavourable biological and clinical risk profile. Preliminary data suggest that in contrast to other haematopoietic
malignancies, such as myelodysplastic syndromes, in CLL allo-HSCT might overcome the adverse prognostic impact of genomic (e.g. TP53 lesions) as well as clinical (e.g. fludarabine resistance) factors. Thus, allo-HSCT may be offered to selected patients as a standard procedure (2).

Of paramount importance for the outcome of allo-HSCT in CLL is the appropriate timing of the transplant. Eligibility for allo-HSCT is usually defined by the quality of response to therapy, as defined by the first and second EBMT criteria. Therefore allo-HSCT is never indicated as part of the first-line treatment of CLL except for those few individuals who have del 17p and/or TP53 mutations and who require treatment (third EBMT criterion). However, large prospective studies of reduced intensity conditioning transplantation (RICT) uniformly show that in CLL the results of allo-HSCT are considerably impaired if the disease is not in remission at the time of transplant (3–5). Thus, allo-HSCT should be performed in a timely fashion, i.e. as soon as the EBMT criteria are met.

2.2 Autologous HSCT
Auto-HSCT, when used for consolidation in first or second remission, does not provide significant benefit over current chemo-immunotherapeutic standard treatments for CLL. Accordingly, there is no standard indication for auto-HSCT in CLL. It may be a clinical option, however, in individual situations, such as transformation (Richter’s syndrome).

3. Conditioning regimens
There is no doubt that the crucial therapeutic principle of allo-HSCT in CLL is graft-versus-leukaemia (GvL) activity. Evidence for this derives from the observation that even in patients with the poorest-risk disease long-term clinical remissions can be observed after allo-HSCT but not with any other treatment modality, and from the fact that - in contrast to auto-HSCT or other intensive therapies - the incidence of relapse seems to decrease over time (6). In addition, the importance of GvL in CLL is indicated by a reduced relapse risk in the presence of chronic graft-versus-host disease (cGvHD) (7), an increased relapse risk associated with the use of

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Table 1: Criteria for poor-risk disease according to the EBMT CLL Transplant Consensus (1)

- Non-response or early relapse (within 12 months) after purine analogue-containing therapy
- Relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (i.e. autologous stem cell transplantation)
- p53 deletion/mutation (del 17p13) requiring treatment

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T-cell depletion (TCD) (8, 9), the efficacy of donor lymphocyte infusions (DLI) (8), and the kinetics of post allo-HSCT minimal residual disease (MRD) (see below). Altogether, there appears to be sound evidence that GvL activity represents the main contributor to durable disease control after allo-HSCT even in poor-risk CLL. Accordingly, long-term disease control can be achieved with a broad range of conditioning intensities. Current evidence is not sufficient to identify any single superior conditioning regimen. The most convincing data supporting allo-HSCT in CLL come from studies of RICT rather than from trials with traditional myeloablative allo-HSCT (10). However, impaired disease control associated with RIC as compared with more intensive conditioning cannot be excluded (6, 7). Thus the optimum choice of conditioning regimens may vary according to the individual situation. In the presence of comorbidity and chemosensitive disease RIC appear to be more appropriate, whereas high-intensity regimens might be preferable in younger patients with good performance status but poorly controlled disease (1). There is no evidence for any clinical benefit of T-cell depletion in CLL.

4. Outcome and role of allogeneic transplants in CLL
The risks of allo-HSCT in patients with CLL are mostly the general risks of transplant and are basically due to GvHD. Toxicity and mortality seem to be influenced by the type of conditioning regimen employed (10). With RIC, reported NRM risk at 4 years post-transplant ranges from 15 to 25% (3–5, 11, 12). As mentioned previously, long-term disease control due to a low rate of late recurrence has been observed in all published series irrespective of donor source and conditioning regimens. Accordingly, a considerable proportion of patients survive leukaemia-free after allo-HSCT, as illustrated by 5-year EFS and OS rates ranging from 30 to 70% in prospective RICT studies (3–5, 11, 12). In summary, cure seems to be possible in up to two-thirds of patients undergoing allo-HSCT for poor-risk CLL.

4.1 Outcome and role of unrelated and alternative transplants in comparison to HLA-identical sibling transplants in CLL
In prospective studies including both matched unrelated donors (UD) and sibling donors (3–5, 11, 12), as well as in a large EBMT registry study (6), significant outcome differences were not evident. Therefore in poor-risk CLL allo-HSCT from a well-matched UD is regarded as standard treatment similar to sibling transplants (1, 2). Transplants from partially matched or mismatched UD have been associated with significantly higher mortality in the EBMT registry study (hazard ratio 1.67) (6). However, with an OS probability of 38% at five years, outcome seems favourable when compared to the results of alternative treatment for patients with poor-risk CLL, justifying...
considering partially matched donor transplants as a clinical option in this risk group. Due to the rarity of the disease and the high average age, in CLL experience with haplo-identical transplants and cord blood transplants is very sparse to date.

4.2 Post-transplant minimal residual disease monitoring and immune intervention in CLL

In CLL, sensitive MRD quantification (i.e. 1 cell in $10^4$ or less) can be obtained by PCR- or flow cytometry-based assays. The decline of the MRD level is often delayed and its close correlation with immune-relevant events strongly supports the assumption that GvL is the crucial contributor to tumour control in allo-HSCT. GvL-induced MRD negativity after allo-HSCT is sustained in the vast majority of cases and is highly predictive of freedom from relapse (5, 13). Furthermore, in CLL quantitative MRD monitoring seems to be a valid instrument for sensitive guidance of pre-emptive immune interventions directed at disease eradication after allo-HSCT, such as the tapering of immunosuppression and the use of DLI (5). Whereas the published evidence strongly suggests that CLL is sensitive to timely pre-emptive immune intervention by modulation of systemic immunosuppression (5, 13, 14), DLI are less effective, in particular after T-replete allo-HSCT and in those patients who are treated with DLI for clinical progression/relapse (reviewed in (10)). Therefore, the best approach to post-transplant immunotherapy (including monoclonal antibodies and alternative B-depleting or immunomodulating agents, such as lenalidomide) in CLL requires further study (10).

5. Outcome and role of autologous transplants in CLL

Auto-HSCT for CLL was developed in the mid-1990s, before fludarabine was approved and before validated genomic prognostic markers were available. Based on favourable pilot data from single centre studies, the hypothesis was that high-dose treatment including myeloablative TBI could possibly cure the disease, in particular if administered early (8). Subsequent multicentre single-arm trials and longer follow-up, however, failed to demonstrate that permanent control of poor-risk CLL is possible with myeloablative auto-HSCT (8, 15, 16). Nevertheless, in the European multicentre studies from the UK (MRD pilot trial) and Germany/Austria (GLLSG CLL3 trial), the median progression free survival (PFS) of patients with CLL intended to undergo first-line auto-HSCT were encouraging at 54 and 68 months, respectively (15, 16).

Therefore, a prospective randomised trial comparing autografting with conventional treatment was performed as a European intergroup effort coordinated by the EBMT, in order to prove whether or not auto-HSCT could provide clinical benefit to patients.
with poor-risk CLL. Patients in first or second remission after conventional chemotherapy for symptomatic CLL were randomised to receive a consolidating auto-HSCT or just observation. Based on 229 patients enrolled, this trial showed that auto-HSCT indeed halved the relapse risk and doubled the time to CLL-specific retreatment, but failed to improve overall survival in comparison to chemotherapy alone (17). Moreover, an inter-trial comparison between the GCLLSG CLL3 study and the fludarabine, cyclophosphamide, rituximab (FCR) arm of the GCLLSG CLL8 study did not reveal a significant benefit of auto-HSCT in terms of time to retreatment (15). Furthermore, even though there is no evidence that the incidence of treatment-related myelodysplastic syndromes and acute myeloblastic leukaemia (t-MDS/AML) after auto-HSCT for CLL exceeds the range reported for standard chemotherapy for B-cell lymphoma, these serious complications must be considered when weighing the benefits and risks of auto-HSCT versus alternative modalities.

In summary, auto-HSCT currently does not have a clearly defined role in the standard treatment algorithm for CLL.

6. Summary and perspectives

Allo-HSCT from related or unrelated donors can be highly effective in otherwise resistant CLL. Therefore it is regarded as a standard treatment option for eligible patients who fulfil accepted criteria for poor-risk disease. Allo-HSCT should be considered before the disease has advanced to a status of complete refractoriness to salvage therapy. Allo-HSCT for CLL should be performed within the frame of a research protocol whenever possible.

In contrast, auto-HSCT currently does not have a clearly defined role in the standard treatment algorithm for CLL.

References


Multiple Choice Questionnaire

To find the correct answer, go to [http://www.esh.org/online-training/handbook/](http://www.esh.org/online-training/handbook/)

1. Female patient, 53 years old, first diagnosis of CLL after known “elevated white blood count” over years, WBC 120 x 10^9/L with no other laboratory abnormalities, no symptoms, no lymphadenopathy, stage Binet A. Which one of the following strategies should be recommended?
   a) Further diagnostic procedures, e.g. bone marrow biopsy
   b) No immediate intervention, observation of course
   c) Chlorambucil
   d) Fludarabine-cyclophosphamide followed by autologous stem cell transplantation

2. In which one of the following situations is allo-HSCT not worth considering?
   a) Diagnosis of CLL with deletion 17p13 without symptoms in a 55-year old patient
   b) Non-response of CLL to fludarabine in a 60-year old patient
   c) Progressive disease 2 years after fludarabine-cyclophosphamide-rituximab in a 62-year old patient without siblings
   d) Relapse of CLL in a 49-year old patient 18 months after auto-HSCT

3. Which one of the following situations might be an indication for auto-HSCT?
   a) Diagnosis of symptomatic CLL with deletion 17p13 in a 55-year old patient
   b) Non-response of CLL to fludarabine in a 60-year old patient
   c) CLL progression 2 years after fludarabine-cyclophosphamide-rituximab in a 62-year old patient
   d) None of the above

4. Which one of the following statements is not correct?
   a) In CLL, the sensitivity of MRD assessment using 4-colour flow cytometry cannot be higher than 1 tumour cell in 10,000 normal cells
b) MRD negativity is frequently achieved after auto-HSCT for CLL and indicates cure.

c) MRD negativity after allo-HSCT for CLL often occurs only after immunomodulating manoeuvres, such as withdrawal of systemic immunosuppression or DLI.

d) MRD negativity one year after allo-HSCT for CLL indicates a favourable outcome.

5. Female patient, 53 years old, refractory after salvage treatment with fludarabine, stage Binet C with 95% BM infiltration, night sweats, moderate lymphadenopathy. FISH karyotype del 11q22, del 17p13. Recommended strategy:

a) Further diagnostic procedures, e.g. mutational status, ZAP70

b) Salvage fludarabine-cyclophosphamide-rituximab

c) Salvage alemtuzumab, followed by allogeneic stem cell transplantation from an HLA-identical sibling or from a matched unrelated donor

d) Autologous transplantation