

* CHAPTER 25

HSCT for chronic lymphocytic leukaemia in adults

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Efforts to develop curative treatment strategies for chronic lymphocytic leukaemia (CLL) have focussed on autologous and allogeneic HSCT during recent years.

1. Indications

In CLL, *allogeneic HSCT* (allo-HSCT) is a possible treatment option for eligible 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 the only therapy with curative potential in CLL. In contrast to conventional treatment, it can provide long-term disease control even in patients with a very unfavourable biological and clinical risk profile. Thus, allo-HSCT may be offered to suitable patients as a standard procedure if disease-specific prospective clinical trial protocols are not available (2).

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

Autologous HSCT (auto-HSCT) is a clinical option for consolidation treatment of patients in first or second remission who are able to withstand high-dose therapy. In the absence of evidence for superiority over effective non-transplant regimens, however, auto-HSCT should be performed in the context of a clinical trial (2).

2. 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 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 relapse incidence seems to decrease over time (Table 2). In addition, GvL effectiveness in CLL is indicated by a reduced relapse risk in the presence of chronic graft-versus-host disease (GvHD) (3), an increased relapse risk associated with the use of T-cell depletion (TCD) (4), efficacy of DLI (4), and post allo-HSCT minimal residual disease (MRD) kinetics (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.

Table 2: Prospective trials of T-replete RIC allo-HSCT in CLL (all phase II)

Study	Houston (11)	Boston (12)	Seattle (10)	DKTSG (9) ^a	DCLLSG (1)
n	39	46	44 ^b 20 ^c	30	44
Age (years)	57 (34–70)	53 (35–67)	56 (44–69)	50 (12–63)	53 (27–63)
Median number of pretreatment lines	n.a.	5	4 3.5	3	4
Refractory at HSCT	28%	57%	45% 57%	46%	20%
Alternative donor ^b	18%	67%	100% 0%	57%	48%
Conditioning	FluCy-Rituximab	FluBu6.4	FluTBI2	FluBu8	FluCy
TRM	30%	17%	22% 20% (2y)	15% (5y)	7% (3y)
Relapse rate	n.a.	48% (2y)	34% 5% (2y)	30% (4y)	33% (3y)
Late relapses (>2 yrs)	0	0	0 0	4	2
EFS	44% (2y) ^d	34% (2y)	44% 75% (2y)	58% (4y)	62% (3y)
OS	64% (2y)	54% (2y)	56% 74% (2y)	69% (4y)	79% (3y)
Follow-up (mo)	27 (4–80)	20 (6–48)	24 (3–63)	44 (25–67)	29 (5–81)

EFS: event-free survival; FluBu6.4: fludarabine 120mg/m² + busulfex 6.4mg/kg; FluBu8: fludarabine 150mg/m² + busulfan 8mg/kg; FluCy: fludarabine 150mg/m² + cyclophosphamide 2,5g/m²; FluTBI2: fludarabine 90mg/m² + total body irradiation 2Gy; n.a.: not available; OS: overall survival; TRM: treatment-related mortality. ^a and unpublished data; ^b matched unrelated donors or mismatched related donors; ^c matched related donors; ^d current progression-free survival

Accordingly, long-term disease control can be achieved with a broad range of conditioning intensities. Current evidence is not sufficient to identify a generally superior conditioning regimen. Considering the quality of trials performed, it appears that the most convincing data supporting allo-HSCT in CLL comes from RIC studies rather than from trials with traditional myeloablative allo-HSCT. However, impaired disease control associated with RIC cannot be ruled out (3). Thus, according to the individual situation, the optimum choice of conditioning regimens may vary: Whereas in the presence of comorbidity and sensitive disease RIC appear to be more appropriate, high-intensity regimens might be preferable in younger patients with good performance status but poorly controlled disease (1). Prospective clinical trials should help to guide the choice of conditioning intensity in allo-HSCT for CLL. Evidence for clinical benefit of T-cell depletion in CLL is lacking. In the majority of published data on autologous stem cell transplants for CLL the

myeloablative regimen contained TBI. The rationale behind this is that CLL cells - similar to other indolent lymphatic neoplasms - are sensitive to irradiation. In the absence of prospective comparisons, however, the best preparative regimen for autografting patients with CLL is still unknown.

3. Outcome and role of autologous transplants in CLL

Auto-HSCT for CLL was pioneered by the Dana-Farber Cancer Center. Patients with advanced CLL underwent myeloablative therapy (TBI/CY) followed by reinfusion of autologous bone marrow (BM) purged with anti-B-cell monoclonal antibodies and complement. Recently updated results on 137 patients show that relapses continued to occur over 10 years of follow-up, translating into a progression-free survival of 30% at 6 years post transplant (4). Similarly, no plateau in the survival curve was evident in registry analyses, such as those performed by the EBMT (5). Moreover, two large uncontrolled trials on auto-HSCT as part of first-line therapy of high-risk CLL (MRC pilot trial and CLL3 study of the German CLL Study Group (GCLLSG)) were characterised by continuous relapses which could occur even after 5 years of follow-up (5, 6). Finally, failure to achieve durable MRD negativity after auto-HSCT implies that complete disease eradication is not possible by this intensive approach in the vast majority of patients (7, 8).

Similar to other diseases, such as multiple myeloma, auto-HSCT could confer a substantial therapeutic benefit in CLL even without being curative. In the MRC and GCLLSG prospective trials, median progression-free survival (PFS) was rather long with 54 and 59 months from study entry, respectively (5, 6). However, similar disease control seems to be possible with modern purine analogue-based combinations. Therefore, a reliable evaluation of the impact of HSCT on the prognosis of CLL requires prospective randomised studies comparing autografting with conventional treatment. Such a trial has been performed as a European intergroup effort coordinated by the EBMT. Patients in first or second remission after conventional chemotherapy for symptomatic CLL were randomised to receive a consolidating auto-HSCT or just observation. This trial has recently finished accrual after randomisation of more than 220 patients, but final results will not be available before 2009.

Although 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 previously for B-cell lymphoma, and also fludarabine-alkylator combinations are associated with an increased risk of t-MDS/AML, this serious complication has to be taken into account when weighing the benefits and risks of auto-HSCT versus alternative modalities.

4. Outcome and role of HLA-identical sibling transplants in CLL

The risks of allo-HSCT in patients with CLL are mostly the general risks of allogeneic HSCT and are basically due to GvHD. Toxicity and mortality seem to be strongly influenced by the type of conditioning regimen employed (3). As pointed out previously, long-term disease control due to a low rate of late recurrences has been observed in all published series (excluding those employing *in vivo* or *ex vivo* T-cell depletion) irrespective of donor source and conditioning regimens used. 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 the prospective RIC T-replete studies published to date (Table 2). In summary, cure seems to be possible in one to two thirds of patients undergoing allo-HSCT for poor-risk CLL.

5. Outcome and role of unrelated and alternative transplants in CLL

In prospective studies including both matched unrelated donors (MUD) and sibling donors significant outcome differences did not become evident (Table 2). Therefore MUD allo-HSCT is regarded as standard treatment similar to sibling transplants in poor-risk CLL (1, 2). Transplants from mismatched donors should be restricted to clinical trials. Due to the rarity of the disease and the high average age, in CLL experience with haploidentical transplants and cord blood transplants is very sparse, and it is unlikely that disease-specific evidence for benefit of these procedures can ever be obtained.

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

In CLL, sensitive (i.e. 1 cell in 10,000 or below) MRD quantification can be obtained by PCR- or flow cytometry-based assays and has strong prognostic impact after both auto- and allo-HSCT. The generally delayed decline of the MRD level and its close correlation with immune-relevant events strongly supports the assumption that GvL activity 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 highly predictive of freedom from relapse, whereas in auto-HSCT MRD negativity is achieved only infrequently and is generally short-lived (7, 8).

Furthermore, in CLL quantitative MRD monitoring seems to be a valid instrument for sensitive guidance of immune interventions directed at disease eradication after allo-HSCT. In contrast to DLI upon clinical relapse which often shows only limited benefit in CLL (9, 10), MRD-triggered pre-emptive DLI can be highly effective (7). However, the best approach to post-transplant immunotherapy (including monoclonal antibodies (11)) in CLL needs further study.

7. Summary and perspectives

To date, there is only limited hope that autotransplantation can cure CLL. Nevertheless, the results of prospective trials suggest that auto-HSCT is capable of exerting profound disease control, especially if employed early. However, until the results of the randomised EBMT Intergroup trial are available, auto-HSCT in CLL has to be considered as an experimental procedure which should not be performed outside of a clinical trial protocol. The combination of auto-HSCT with alternative innovative approaches, such as alemtuzumab *in vivo* purging or rituximab-purine analogue combinations, might open new perspectives for long-term and eventually durable disease control.

Allo-HSCT from matched 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. Due to the absence of controlled trials in defined disease settings, however, it is unclear what the real impact of *allo-HSCT* in the treatment of CLL might be, and whether it can change the natural history of poor-risk CLL. The German CLL Study Group is currently conducting a randomised phase-III trial addressing these issues as well as optimum timing of transplantation.

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Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **Female patient, 53 years old, first diagnosis of CLL after known "elevated white blood count" over years, WBC 120 x 10⁹/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 auto-HSCT
2. **In which one of the following situations allo-HSCT is *not* worth being considered?**
 - 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) CLL progression 2 years after fludarabine-cyclophosphamide-rituximab in a 62-year old patient without siblings
 - d) CLL relapse 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) First remission of ZAP70-positive CLL after 3 cycles of fludarabine-cyclophosphamide in a 49-year old patient within a clinical protocol
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- 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 after allo-HSCT for CLL occurring after immunomodulating manoeuvres is generally not durable
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- 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 allo-HSCT only in case of response ..
 - d) Salvage alemtuzumab, followed by allo-HSCT also in case of refractory disease