

* CHAPTER 29

HSCT for low-grade non-Hodgkin's lymphoma in adults

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1. Introduction

The classification of the non-Hodgkin's lymphomas (NHLs) has been a challenge for pathologists as well as practising physicians. The World Health Organization (WHO) lymphoma classification is based upon cell of origin and pathophysiology of the lymphoma and does not include the terminology "low-grade lymphoma". This is a clinical and not pathologic term, and defines those lymphomas which tend to grow and spread slowly and produce few symptoms. Follicular lymphoma (FL) is by far the most common of the low-grade lymphomas and is the second most common subtype of lymphoma worldwide, accounting for approximately 20% of malignant lymphomas in adults, but 40% of all lymphomas diagnosed in Western Europe and the USA. Follicular lymphoma affects predominantly adults, with a median age of 59 years and rarely occurs in individuals under age 20 years.

Although low-grade NHLs are incurable, patients may live for many years. Ten-year survival for Stages I and II is between 60 and 80%. Five- and ten-year median survival for those diagnosed with Stage III disease is 60 and 40% respectively. Five- and ten-year median survival for those diagnosed with Stage IV disease is 50 and 10% respectively. Until recently there was little evidence that the natural history of FL had changed over the last 30 years from the median survival of 10 years from diagnosis, but this may be changing with the introduction of monoclonal antibodies in combination with chemotherapy, with more recent data suggesting that with improvements in treatment the median survival is now 12–14 years. The clinical course is extremely variable, with some patients having an extremely aggressive course and death within one year, while others may live for more than 20 years and never require therapy. The follicular lymphoma international prognostic index (FLIPI) is a five factor prognostic index based upon the clinical characteristics age, stage, number of nodal sites, haemoglobin and LDH level, and defines three prognostic risk groups of almost equal numbers of patients (1). This tool is useful in assessing the likely need for early treatment of patients and potential outcome, as well as in comparing the outcomes of different clinical trials.

Multiple treatment approaches exist for advanced stage low-grade lymphomas, and since there is no clearly defined treatment algorithm for most patients with indolent lymphomas optimal care is that eligible patients should be included whenever possible in clinical trials. Patients remaining on an expectant course (watch and wait) should be followed every three months for history, physical examination and blood tests, including LDH, and special attention should be paid to any change in symptoms that might be suggestive of histologic transformation. Once transformation occurs, these patients should be treated as a high-grade lymphoma. Expectant management is the treatment of choice for asymptomatic patients with

low bulk disease until clear indications for initiation of treatment are seen, except for those patients enrolled in clinical trials assessing the impact of early therapy. This approach is based upon the demonstration of no survival advantage for institution of immediate compared to deferred treatment until time of progression, a finding confirmed by three randomised trials. A major clinical trial question is whether identification of clinical or molecular risk factors can identify which patients are candidates for early therapy. A survival predictor score has also been developed from gene expression profiling studies. A major component of the gene expression prognostic signature is related to immune cells in the tumour microenvironment. Future guidelines for treatment may well be based upon clinical staging systems, genetic profiles and immune response signatures, but these factors do not yet help us to decide who should have immediate therapy, and decisions to treat with approaches including transplant should not be based on such measures except in the clinical trial setting. Treatment is indicated in patients with symptomatic disease, bulky lymphadenopathy and/or splenomegaly, risk of local compressive disease, marrow compromise or rapid disease progression. Once indicated, numerous treatment approaches are available. Options range from a watch and wait expectant management approach, to single agent chemotherapy or monoclonal antibody therapy with rituximab, to combination chemo-immunotherapy, with use of autologous or allogeneic transplant. [Table 1](#) summarises the currently accepted indications for HSCT in low-grade lymphoma.

Table 1: Indications for transplantation in low-grade lymphoma

Disease	Disease status	Allo		Auto
		Sibling donor	Alternative donor	
Low-grade NHL	CR1	NR	NR	CP
	Relapse, CR2, CR3	CP	D	S

S: in standard use for selected patients; CP: to be undertaken in approved Clinical Protocols; D: developmental or pilot studies can be approved in specialist units; NR: not generally recommended

2. The role of autologous transplant in low-grade lymphomas

2.1. Relapsed disease (Table 2)

The use of high-dose chemotherapy with autologous transplant in the treatment of low-grade lymphomas has not yet been fully established. The rationale for considering transplantation is that the disease is incurable using standard approaches and young patients with indolent lymphomas will die of their disease. Promising results have

Table 2: Autologous transplant for relapsed low-grade lymphoma

Author	N	Follow-up (months)	OS (95% CI)	EFS (95% CI)	PFS (95% CI)	TRM %	Reference
Freedman	153	96	66 (57-74)		42 (30-51)	1	(2)
Cortelazzo	103	36	47 (36-59)	61 (48-72)	64 (50-74)	1	(3)
Bierman	100	48	65 (54-75)		44 (33-55)	6	(4)
Colombat	42	60	83	58		7	(5)
Schouten	46	69					(6)
	22 unpurged		71 (52-91)		58 (37-79)	12.5	
	24 purged		77 (60-95)		55 (34-74)	8	

been observed in a number of phase II studies (2–5). The EBMT sponsored CUP study (conventional chemotherapy, unpurged, purged autograft) is the only prospective randomised trial to assess the role of autologous HSCT in patients with relapsed FL (6). Purging was examined because patients with follicular lymphoma, frequently have significant bone marrow involvement. The results of the study demonstrated a PFS advantage and suggest an OS advantage of autologous transplant over conventional chemotherapy, with 4 year OS of 46% for the chemotherapy arm, versus 71% for the unpurged and 77% for the purged autologous transplant arms, with no benefit observed for those patients who underwent purging. There is some concern that the study was closed early because of slow accrual, with 140 of the planned 250 patients accrued and only 89 randomised. However, the results of the CUP trial are generally in line with that observed in the phase II studies, which include larger numbers and for which longer follow up is available. A major concern relates to the risk of development of secondary myelodysplasia/acute myeloid leukaemia. This complication appears to be decreased with the use of chemotherapy-only conditioning regimens without TBI.

Based upon the results of the CUP trial and the encouraging results of the phase II studies, autologous transplant has become standard treatment (S) for patients with relapsed follicular lymphoma who are deemed to be high-risk, although precise criteria that define such “high-risk” patients are lacking. Patients with low-grade lymphomas who are potentially suitable candidates for transplantation should be referred to a transplant centre early to discuss the potential role and timing of transplantation. Best results are seen when transplantation is considered before the disease become chemo-refractory since high dose therapy and autologous transplant

is an effective treatment approach for younger patients with chemo-responsive relapsed disease. Autologous transplant approaches in this disease setting must always be considered in the context of the improving results that are being seen with salvage therapy alone.

2.2 Autologous transplant as consolidation of first remission

The role of high dose therapy and autologous HSCT in FL patients during first remission has been examined in three phase III randomised trials (7–9). The German low-grade study group (GLSG) trial (7) recruited 307 patients up to 60 years of age and patients who responded after induction chemotherapy with 2 cycles of CHOP or mitoxantrone-chlorambucil-prednisone (MCP) were randomised to autologous SCT or interferon (IFN)-alpha maintenance. Among 240 evaluable patients, the 5-year PFS was 64.7% after autologous transplant, and 33.3% in the IFN-alpha arm ($p < 0.0001$). Acute toxicity was higher in the autologous transplant group, but early mortality was below 2.5% in both study arms. Longer follow-up is necessary to determine the effect of autologous transplant on OS. In the Groupe Ouest Est des Leucémies Aigües et des Maladies du Sang (GOELAMS) study, 172 newly diagnosed advanced FL patients were randomised either to cyclophosphamide, doxorubicin, teniposide, prednisone, (CHVP) and IFN-alpha or to high-dose therapy followed by purged autologous transplant (8). Patients treated with high-dose therapy and autologous transplant had a higher response rate than patients who received chemotherapy and IFN-alpha (81 versus 69%, $p=0.045$) and a longer median PFS (not reached versus 45 months), but this did not translate into a better OS due to an excess of secondary malignancies after autologous transplant. A subgroup of patients with a significantly higher event-free survival rate could be identified using the FLIPI. The Groupe Etude Lymphoma Folliculaire (GELF) 94 study enrolled 401 previously untreated advanced stage FL patients who were randomised to receive CHVP plus IFN-alpha compared with four courses of CHOP followed by high dose therapy with total body irradiation (TBI) and autologous HSCT. Response rates were similar in both groups (79 and 78% respectively) and 87% of eligible patients underwent autologous HSCT. Intent-to-treat analysis after a median follow-up of 7.5 years showed no difference between the two arms for OS ($p=0.53$) or PFS ($p=0.11$). Long-term follow-up demonstrated no statistically significant benefit in favour of first-line auto-HSCT in patients with follicular lymphoma, which they conclude should be reserved for relapsed patients. In view of these results, autologous HSCT should be used in first remission only in the setting of clinical trials (CP).

3. Role and outcome of allogeneic HSCT for low-grade lymphoma

3.1. HLA identical sibling transplant and unrelated donors

There is a trend towards increasing use of allogeneic transplant in the management of low-grade lymphomas. There have been no randomised controlled trials in this disease setting, but long term PFS has been observed in patients with low-grade NHLs after allogeneic transplant (10–12) as outlined in Table 3. In a report of the International Bone Marrow Transplant Registry (IBMTR), results are described for 904 patients with FL, 176 of whom underwent allogeneic transplant from HLA matched sibling, 131 patients underwent autologous transplant using purged stem cells and 597 using unpurged autologous stem cells (13). The treatment related mortality (TRM) in these three groups was 30, 14 and 8% respectively, disease recurrence in 21, 43 and 58% and 5 year overall survival was 51, 62 and 55% respectively. The use of TBI containing regimens was associated with increased TRM but decreased risk of relapse. The use of HLA identical sibling allogeneic transplant was associated with increased TRM - compared to autologous transplantation - but significantly lower risk of disease recurrence in keeping with a graft versus lymphoma effect in this disease. Long term PFS has been observed after allogeneic SCT even in patients with refractory FL (12). In 29 FL patients, 11 of whom had refractory disease, the non-relapse mortality was 24% and there was a 23% incidence of relapse. Twenty of these patients underwent allogeneic transplantation from HLA identical siblings. The five year OS was 58% with 53% event free survival. A group of patients with very poor outcome are those patients who have relapsed after previous autologous transplant. The outcome following myeloablative allogeneic transplant of 114 such patients have been reported from the IBMTR (14). The treatment related mortality was 22% and

Table 3: Allogeneic transplant for low-grade lymphoma

Histology	No. of patients	Median age (range)	Status	Conditioning	Outcome	TRM (%)	Reference
FL 6 SLL 4	10	42 (31–55)	3 sensitive 8 refractory	CY/TBI	68% PFS at 2 years	30	(10)
FL 93 SLL 20	113	38 (15–61)	66 sensitive 39 refractory	TBI 93 Non TBI 20	49% PFS at 3 years	40	(11)
FL 29	29	42 (20–53)	6 induction failure 18 sensitive 6 refractory	27 TBI	53% PFS at 5 years	24	(12)

FL: follicular lymphoma; SLL: small lymphocytic lymphoma

the probability of disease progression was 52% at 3 years. The use of TBI conditioning regimens and achievement of CR at the time of allogeneic SCT were associated with improved outcome. In view of the high TRM and the long disease course allogeneic transplant from HLA matched siblings is not recommended in first CR or PR (NR).

3.2. Reduced intensity HSCT

The use of reduced intensity conditioning regimens results in decreased TRM and appears to be associated with improved outcome. There have been no randomised clinical trials, but a number of phase II studies have clearly demonstrated evidence of a graft versus lymphoma effect that can be exploited in low-grade NHLs, as outlined in Table 4 (15–23). In many studies results are combined together for patients with low-grade and high-grade NHL, and for HLA matched siblings and unrelated donors, making full comparison of outcomes in specific subgroups impossible. The outcome following reduced intensity conditioning transplant regimen a immunosuppressive

Table 4: Reduced intensity conditioning allogeneic transplant for low-grade lymphoma

No. of patients	Prior treatment Median (range)	Conditioning	GvHD (%)	Graft failure	Outcome	Ref.
23	3 (2–6)	FLU/BU/ATG	Acute 34	0	40% PFS at 3 yrs	(15)
20	2 (1–5)	FLU/CY/rituximab	Acute 20 Chronic 64	0	84% PFS at 2 yrs	(16)
13	3 (1–7)	200 cGY TBI	Acute 54 Chronic 62	1	7 CR	(17)
44	3 (0–6)	FLU/MEL/alemtuzumab	Acute 16 Chronic 2	1	22 CR 11 PR	(18)
88 (mixed histologies)	4 (2–6)	FLU/MEL/alemtuzumab	Acute 30	4	73% OS at 3 yrs (low-grade)	(19)
65	2 (1–6) 11% prior autologous SCT	BEAM/alemtuzumab	Acute 17 Chronic 17	3	69% PFS at 2 yrs	(20)
47	62% prior autologous transplant	FLU/MEL/alemtuzumab	Acute 23 Chronic 6	2	75% OS at 1 yr 61% PFS at 1 yr	(22)
188	3 48% prior autologous transplant	Various	Acute 37 Chronic 17	6	25% TRM 50% OS at 2 yrs	(23)

FLU: fludarabine; MEL: melphalan

therapy has been reported for 81 patients with lymphoma including 41 with low-grade NHL (19). Patients received a conditioning regimen consisting of alemtuzumab, fludarabine and melphalan, and received short course cyclosporin as GvHD prophylaxis. The use of this conditioning regimen was associated with a low incidence of GvHD and the treatment related mortality was decreased in patients with low-grade compared to higher grade histology. The three-year progression free survival was 65% for patients with low-grade lymphoma.

3.3. Role of haploidentical donors and cord blood transplant in low-grade lymphoma

The use of alternative donor sources including haploidentical transplant and cord blood transplant are considered developmental and should be considered for selected patients only in specialised centres.

4. Post-transplant management

4.1. Nature and role of cellular or chemotherapy post-transplant

The use of monoclonal antibodies to attempt to eradicate any residual lymphoma cells after autologous or allogeneic transplant is being examined in ongoing clinical trials. Donor lymphocyte infusion (DLI) are effective in treating relapse after allogeneic transplant provides very strong evidence for a graft versus lymphoma effect that can be exploited in indolent lymphomas.

4.2. Nature and role of minimal residual disease monitoring after transplant

Detection of MRD has been a useful surrogate marker for tracking long-term PFS in patients examining the autologous stem cells or serial samples after both autologous and allogeneic transplant (24–27). The increasing use of therapeutic monoclonal antibodies may make the use of peripheral blood rather than bone marrow a less useful cell source for monitoring MRD, since monoclonal antibodies appear to clear peripheral blood very successfully. There is concern using detection of the BCL-2/IgH rearrangement as a marker for MRD detection in FL since this rearrangement can be found in the blood of many healthy individuals, but these cells seem to be cleared by chemotherapy so that when MRD is detected after chemotherapy, it is usually from the malignant clone (28). Monitoring and treatment of MRD in low-grade lymphomas is indicated in the setting of clinical trials.

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Multiple Choice Questionnaire

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

1. Which statement *is not* true regarding the CUP trial?

- a) The study demonstrated a PFS advantage of ASCT over chemotherapy...
- b) Purging was beneficial
- c) There is a concern that the study was closed early because of slow accrual.....
- d) This is the only prospective randomised trial to assess ASCT in relapsed FL.....

2. Which statement *is not* true regarding auto-HSCT for FL?

- a) Auto-HSCT has become standard treatment for pts with relapsed FL.....
- b) Best results are seen when auto-HSCT is considered before the disease becomes chemo refractory
- c) Auto-HSCT should be used in first remission only in clinical trials.....
- d) Secondary MDS/AML is less frequent if the conditioning contains TBI ...

3. Which process results in the highest treatment related mortality in relapsed FL?

- a) Allogeneic transplant from with standard conditioning
- b) Autologous transplant using purged stem cells
- c) Autologous transplant using unpurged stem cells
- d) Allogeneic transplant with reduced intensity conditioning

4. Which sentence is true?

- a) Randomised trials demonstrated long term PFS following allo-SCT in FL .
- b) Reduced intensity conditioning does not decrease TRM
- c) There is a strong graft versus low-grade lymphoma effect
- d) DLI is not effective in FL.....

5. Which of the following transplant should be considered standard of care in FL?

- a) Autologous transplant without purging in chemosensitive relapse.....

- b) Autologous transplant without purging in CR1.....
- c) Alternative donor transplant in CR2.....
- d) Sibling donor transplant in CR1.....