REVIEW

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Follicular Lymphoma: An Evidence-Based Review

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Clinical research examining the role of hematopoietic stem cell transplantation (SCT) in the therapy of follicular non-Hodgkin lymphoma in adults is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations reached unanimously by a panel of follicular lymphoma experts are: (1) autologous SCT is recommended as salvage therapy based on pre-rituximab data, with a significant improvement in overall survival (OS) and progression-free (PFS) survival; (2) autologous SCT is not recommended as first-line treatment for most patients because of no significant improvement in OS; (3) autologous SCT is recommended for transformed follicular lymphoma patients; (4) reduced intensity conditioning before allogeneic SCT appears to be an acceptable alternative to myeloablative regimens; (5) an HLA-matched unrelated donor appears to be as effective an HLA-matched related donor for reduced intensity conditioning allogeneic SCT. There are insufficient data to make a recommendation on the use of autologous SCT after rituximab-based salvage therapy. Eleven areas of needed research in the treatment of follicular lymphoma with SCT were identified and are presented in the review.

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INTRODUCTION

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of hematopoietic stem cell transplantation (SCT) in the therapy of selected diseases. Seven previous reviews have been published in *Biology of Blood and Marrow Transplantation* (*BBMT*) on the use of SCT in the therapy of: diffuse large B cell non-Hodgkin lymphoma (NHL) [1], multiple myeloma [2], pediatric acute lymphoblastic leukemia (ALL) [3], adult ALL [4], pediatric acute myelogenous leukemia (AML) [5], adult AML [6], and myelodysplastic syndromes (MDS) [7]. The goals of the current review are to assemble and critically evaluate evidence regarding the role of SCT in the therapy of follicular lymphoma (FL), make treatment recommendations based on the available evidence, and identify areas of needed research.

EXPERT PANEL SELECTION

To achieve an appropriate balance, disease-specific experts who have published studies using SCT and other therapies are invited to join the independent expert panel that examines the literature and provides subsequent treatment recommendations based on the

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available evidence. For the current evidence-based review, potential panelists were considered based on their expertise in FL treatment. Potential panelists are restricted to U.S.-based institutions for 2 reasons: (1) ease of logistics in convening teleconferences, and (2) differences in the health care systems and health insurance coverage between the United States and other countries (including Canada, Europe, etc.) that may result in different expert recommendations based on considerations of costs and access to care.

LITERATURE SEARCH METHODOLOGY

PubMed and Medline, the Web sites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were searched on June 10, 2008, using the search terms "follicular lymphoma" and "transplantation" limited to "human trials," "English language," and a publication date of 1990 or later. Updated searches were conducted on January 12, 2009, and June 9, 2009. In addition to the online database searches, a manual search of the reference lists of reviews and included articles was conducted. Papers published before 1990, that included fewer than 25 FL patients, or were not peer reviewed were excluded. Also excluded were editorials, letters to the editor, Phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates. Abstracts and presentations at national or international meetings were not included as evidence in this review for reasons previously described [3]. To be included in this evidence-based review, at least 65% of a study's patients had to have FL, unless the results were stratified by histologic subtype of lymphoma.

QUALITATIVE AND QUANTITATIVE GRADING OF THE EVIDENCE

The hierarchy of evidence, including a grading system for the quality and strength of the evidence and strength of each treatment recommendation, was published as an editorial policy statement in *BBMT* in 2005 [8]. Tables 1 and 2, reprinted from the policy statement, define criteria used to grade the studies that were included in this review and criteria to grade the treatment recommendations, respectively. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan also were considered in evaluating the studies. Clinical studies are described in the review's text and tables with sufficient detail to give a concise summary of study design, sample size, eligibility criteria, treatment schema, and patient outcomes.

Table 1. Grading the Quality of Design and Strength of Evidence

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2−	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (eg, case reports, case series)
4	Expert opinion

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All data in the text and tables were abstracted from the original manuscripts by the first author (D.O.), and double-checked for accuracy and clarity by two other authors (T.H. and P.L.M.). Some articles contained inconsistencies within the data reported; the data most consistent with the text of the article were included in this review. The authors D.O., T.H., and P.L.M. take responsibility if errors remain.

TREATMENT RECOMMENDATIONS

The strength of this review is in the grading of the strength of the evidence and quality of the study

Table 2. Grading the Strength of the Treatment Recommendation

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

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Table 3. Summary of Treatment Recommendations Made by the Expert Panel for Follicular Non-Hodgkin Lymphoma

Indication for SCT	Treatment Recommendation Grade*	Highest Level of Evidence†	Reference No.‡	Treatment Recommendation Comments
AUTOLOGOUS SCT VERSUS NONTRANSPLANTATION THERAPY				
Autologous SCT versus Nontransplantation therapy as first-line treatment	A	1++	9	Although there is consistent improvement in PFS/EFS with autologous SCT, it is not recommended for most patients because of no significant improvement in overall survival (OS), a higher incidence of secondary MDS/AML, and a lack of comparative data with rituximab-containing regimens. Longer follow-up may be needed to identify differences in OS.
Autologous SCT versus nontransplantation therapy as salvage treatment with rituximab as part of induction and/or salvage therapy	No recommendation	2+	16	With only one retrospective study, there are insufficient data to make a recommendation on the use of autologous SCT versus nontransplantation therapy as salvage treatment for patients who have had rituximab as part of their induction and/or salvage therapy.
Autologous SCT versus nontransplantation therapy as salvage treatment without rituximab as part of induction and/or salvage therapy	A	1-	17	Based on pre-rituximab data, there is a statistically significant improvement in OS and PFS using autologous SCT as salvage therapy.
Autologous SCT versus nontransplantation therapy as treatment for transformed FL	D	3		Based on expert opinion and accepted clinical practice, autologous SCT is recommended for transformed follicular lymphoma patients.
DONOR SELECTION				
Autologous SCT versus myeloablative Allogeneic SCT	No recommendation	2+	20-23	There are insufficient data to recommend one option over the other; both appear to have a survival benefit, but have competing risks. Comparison of these two techniques is biased by different patient selection criteria.
Autologous SCT versus RIC/NMA Allogeneic SCT	No recommendation			There are currently no data available to make a recommendation regarding the use of RIC/NMA allogeneic SCT versus autologous SCT. Comparison of these two techniques is biased by different patient selection criteria.
AUTOLOGOUS SCT				
Autologous SCT as first-line versus salvage treatment (Timing of SCT)	No recommendation	2-	25	With only one study, there are insufficient data to make a recommendation regarding the efficacy of autologous SCT as first-line versus salvage therapy.
Rituximab versus no rituximab as part of induction and/or salvage treatment prior to Autologous SCT	No recommendation	2-	26-28	Because of conflicting data, a recommendation on the use of rituximab as part of induction and/or salvage therapy prior to autologous SCT cannot be made.
Purged versus unpurged Autologous SCT	No recommendation	1-	17	There are insufficient data to make a recommendation regarding purging in autologous SCT.
Comparison of high-dose regimens for Autologous SCT	No recommendation	2+	30-32	There are insufficient data to recommend one high dose regimen over another. TBI-containing regimens are usually avoided because of a concern for a higher risk of secondary MDS/AML.
ALLOGENEIC SCT				
Myeloablative versus reduced-intensity Allogeneic SCT	No recommendation	2++	33	There are insufficient data to make a recommendation for one conditioning regimen intensity over another for allogeneic SCT. Based on one study and expert opinion, RIC appears to be an acceptable alternative approach. Based on expert opinion, an HLA-matched unrelated donor allogeneic SCT appears to be as effective as an HLA-matched related donor allogeneic SCT using RIC.

AML indicates acute myelogenous leukemia; EFS, event-free survival; FL, follicular lymphoma; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; NMA, nonmyeloablative; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning; SCT, stem cell transplantation; TBI, total body irradiation.

*Definitions: Grade of Recommendation (Table 2): (A) At least 1 meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results; (B) A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+; (C) A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++; (D) Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

†Definitions: Levels of Evidence (Table 1): 1++ High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias; 1+ Well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1− Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2++ High-quality systematic reviews of case-control or cohort studies; or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal. 2+ Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal; 2− Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal; 3 Nonanalytic studies (eg, case reports, case series); 4 Expert opinion.

‡The references listed represent the *highest level* of evidence used to make the treatment recommendation and are *not* inclusive of all evidence described in the review.

designs as described in the text and summary tables included in each major section. Table 3 contains the summary of consensus treatment recommendations by the FL expert panel based on the summarized evidence. The consensus process involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop initial treatment recommendations according to the categories in Table 2. The information is summarized in Table 3 by the primary authors and distributed to the panelists for additional review and clarification. Any changes suggested by an individual panelist are circulated for review and approval by all panelists. This iterative process concludes when a final version of the Treatment Recommendations table is approved by all panelists. After the final draft of the review is approved by the disease-specific expert panel, it undergoes peer review, first by the ASBMT Steering Committee for Evidence-Based Reviews, then by the ASBMT Executive Committee before submission to the journal. Any changes requested during the peer-review process must be reviewed and approved by all disease-specific expert panelists.

FORMAT OF THE REVIEW

Evidence is taken from studies that included FL patients ≥15 years of age. Studies of "low-grade lymphoma" or "indolent lymphoma" patients are included when FL was the most common subtype included under those broader terms. For each section of the review, a summary paragraph provides an overall description of the number and types of studies included as evidence, as well as a brief synopsis of outcomes. The design of each study is described in the text and, unless otherwise noted, an accompanying summary table in each section presents additional design and methodology information and patient outcomes for each study. In each section of this review, the highest quality studies are presented first; studies of equal quality are presented in descending order by study population size. When descriptive information about a study is not included in the table, such as the median number of prior chemotherapy regimens or median time from diagnosis to SCT, it is because the information was not provided in the article.

AUTOLOGOUS SCT VERSUS NONTRANSPLANTATION THERAPY

This section describes several studies that compare the impact of first-line or salvage autologous SCT versus nontransplantation therapy on patient outcomes. Table 4 presents a summary of the outcomes data from these studies.

First-Line Autologous SCT versus Nontransplantation Therapy ± Rituximab

There are five randomized studies and one nonrandomized cohort study that examined first-line autologous SCT versus nontransplantation therapy. The quality of these studies ranged from 1++ to 2− (as per Table 1). Two of the randomized studies included the use of rituximab for stem cell mobilization, *in vivo* purging, or as a component of induction or high-dose therapy regimens; the remaining four studies in this section did not use rituximab. Although the reported follow-up times varied from 4 to 9 years, in all five randomized studies there was a significant positive impact on event-free survival (EFS) or progression-free survival (PFS), but no difference in overall survival (OS) for patients undergoing first-line autologous SCT versus those who underwent standard therapy.

Studies of First-Line Autologous SCT versus Nontransplantation Therapy (with Rituximab)

Ladetto et al. [9] reported the results of a prospective, multicenter study by the Gruppo Italiano Trapianto di Midollo Osseo/Intergruppo Italiano Linformi (GITMO/IIL) of 136 adult (18-60 years) patients with high-risk FL at diagnosis, who were randomized to receive either six cycles of cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) followed by six cycles of rituximab (CHOP-R, n = 66) or rituximab supplemented high-dose sequential chemotherapy (R-HDS) followed by an autologous peripheral blood stem cell transplantation (PBSCT) purged *in vivo* with rituximab (n = 68). Two CHOP-R patients were not included in the analysis because of enrollment errors. There were no significant differences in patient or disease characteristics between the two groups. The CHOP-R and R-HDS protocols were completed by 71% and 79% of patients, respectively. Complete remission (CR) rates were 62% and 85% ($P < .001$), and partial remission (PR) rates were 8% and 5% in the CHOP-R and R-HDS groups, respectively. Analyses were based on intention to treat. The R-HDS patients had a significantly higher 4-year EFS, but not OS, than the CHOP-R patients. Figure 1 presents the probability of EFS for patients in the two treatment arms.

Lenz et al. [10] presented the outcomes of a prospective, multicenter trial by the German Low Grade Lymphoma Study Group (GLSG) of 440 adult (27-64 years) patients with indolent lymphoma (75% follicular, 17% mantle cell, 7% lymphoplasmacytic, 2% marginal-zone). After CHOP or CHOP-R induction therapy, patients were randomized to receive either interferon-α (IFN-α) maintenance or high-dose cyclophosphamide (Cy) + total body

Table 4. Patient Characteristics and Outcomes from Autologous SCT versus Nontransplantation Therapy Studies

Study Design			Patient Outcomes				
(Ref #), Qual. and Strength of Evidence,* and Patient Population	Protocols	Diagnosis or FL Subtype (at Dx unless Stated)	Study Groups (n) (Med Follow-up [Range])	(Interval) % TRM (Significance)	(Interval) % DFS/RFS/PFS/EFS (Significance)	(Interval) % OS (Significance)	(Interval) % MDS/AML (Significance)
FIRST-LINE AUTO SCT VERSUS NONTRANSPLANTATION THERAPY (WITH RITUXIMAB)							
[9] Ladetto et al. 2008 1++ 2000-2005 GITMO/IIL Multictr (30) Enrolled n = 136 Randomized n = 134 Med Age (range): 51 y (22-59y)	Auto PBSCT (R-HDS) *Induction*: APO *Purging*: Ritux *HDT*: Mito + Mel Non-SCT (CHOP-R) CHOP + Ritux	FL 100% FLIPI ≥3 58% Stage IV 88%	(ITT) Auto PBSCT (68) Non-SCT (66) [4.3 y (not stated)]	Not Stated	(4-year EFS) 61% 28% ($P < .001$)	(4-year OS) 81% 80% ($P = .96$)	(4-year) 6.6% 1.7% ($P = .111$)
[10] Lenz et al. 2004 1+ 1996-2002 GLSG Multictr (130) Randomized n = 440 Evaluable n = 431 (All patients) Med Age (range): 50.9 y (27-64y)	*Induction:* CHOP or CHOP-R Auto PBSCT *PBSC Mobil:* Chemo + GF *HDT:* Cy + TBI Chemo + IFN-α CHOP-like + IFN-α maint	FL 75% MC 17% LPL 6.5% Marginal 1.5% Stage IV 77%	(As treated) Auto PBSCT (195) [3.8 y (not stated)] Chemo + IFN-α (236) [3.7 y (not stated)]	Not Stated	(5-year PFS) 60.2% CI 51.1- 69.3% 31.6% CI 24.5%-38.8% ($P < .0001$)	Not Stated	(5-year) 3.8% 0% ($P = .0248$)
[11] Sebban et al. 2006 1+ 1994-2001 GELA Multictr (71) Enrolled n = 402 Randomized n = 401 Confirmed FL n = 339 (All patients) Med Age (range): 49 y (<61y)	Auto PBSCT *Induction:* CHOP *PBSC Mobil:* Chemo + GF *HDT:* Cy + VP-16 + f-TBI Chemo + IFN-α CHVP+ INF-α + same maint	FL 95% DLBCL 2.5% MC 1.5% SLL 1% FLIPI Auto PBSCT ≥3 70% Chemo + IFN-α ≥3 68%	(ITT) Auto PBSCT (192) (FL only, 167) Chemo + IFN-α (209) (FL only, 172) (7.7 y [not stated])	Not Stated	(7-year EFS) (FL only) 40% CI 33%-48% 29% CI 21%-36% ($P = .05$)	(7-year OS) (All patients) 76% CI 69%-82% 71% CI 65%-71% ($P = .53$)	(7-year) (All patients) 1% 2% (P not stated)
[12] Lenz et al. 2004 1+ 1996-2000 GLSG Multictr (130) Enrolled n = 375 FL Enrolled n = 307 FL Included n = 240 Med Age (range): 49.1 y (26-59y)	*Induction:* CHOP or MCP Auto PBSCT *PBSC Mobil:* Chemo + GF *HDT:* Cy + TBI Chemo + IFN-α CHOP + IFN-α maint	FL 100% Stage IV 74.2%	(As treated) Auto PBSCT (114) Chemo + IFN-α (126) (4.2 y [not stated])	(Not stated) 1.8% Not stated	(5-year PFS) 64.7% CI 54.6%-74.8% 33.3% CI 24.3%-42.3% ($P < .0001$)	Not Stated	Not Stated

(*Continued*)

Table 4. (*Continued*)

Study Design				Patient Outcomes			
(Ref #), Qual. and Strength of Evidence,* and Patient Population	Protocols	Diagnosis or FL Subtype (at Dx unless Stated)	Study Groups (n) (Med Follow-up [Range])	(Interval) % TRM (Significance)	(Interval) % DFS/RFS/PFS/EFS (Significance)	(Interval) % OS (Significance)	(Interval) % MDS/AML (Significance)
[13] Gyan et al. 2009 1+ 1994-2001 GOELAMS Multictr (25) Enrolled n = 172 Randomized n = 166 Med Age (range): Auto SCT 51 y (32-60y) Chemo+IFN-α 50 y (29-61y)	Auto PBSCT *Induction*: VCAP± DHAP (salvage) *PBSC Mobil*: Chemo Purging varied by center *HDT:* Cy + f-TBI Chemo+IFN-α *Induction:* CHVP *Maint:* CHVP+ INF-α	FL 100% FLIPI Auto SCT ≥3 70% Chemo+IFN-α ≥3 71.5%	(ITT) Auto SCT (86) Chemo+IFN-α (80) (9 y [not stated])	(Not stated) 0% 0% (*P* < .03)	(9-year EFS) 56% CI 45%-67% 39% 28-50% (*P* = .55)	(9-year OS) 76% CI 67%-85% 80% CI 72-89% (*P* not stated)	(9-year) 7% 1% (*P* not stated)
[15] Horning et al. 2001 2− 1988-1994 Single Ctr Auto SCT n = 37 1962-1988 Historic Control Non-SCT n = 188 Med Age (range): Auto SCT 37 y (26-49y) Non-SCT All ≤50 y (not stated) Med Dx to SCT (range): 0.8 y (not stated)	Auto SCT *Induction:* CVP† 65% + other chemo combo 35% *BM Mobil*: GF Ex vivo *Purging:* mAbs + Comp *HDT:* Cy + VP-16 + f-TBI Non-SCT Not specified	FL 100% Status at SCT CR1 22% PR1 78%	 Auto SCT (37) Non-SCT (188) (6.5 y [4 -12 y])	(Not stated) 5% Not Stated	Not Stated	(5-year OS) 92% 88% (*P* Not stated)	(69 mos) 5% Not Stated
SALVAGE AUTO SCT VERSUS NON-TRANSPLANTATION THERAPY (± RITUXIMAB)							
[16] Sebban et al. 2008 2+ GELA GELF-86 & GELF-94 Multictr Retrospective Analyzed n = 246 Med age (range not stated): Auto after Ritux 49 y Auto after No Ritux 44 y Chemo+Ritux 52.5 y Chemo-only 52 y	*Salvage:* DHAP or ICE or MINE or Flu-based ± Ritux *HDT:* VP-16 + Cy + TBI or BEAM No Ritux maint. post-HDT	FL 100%	 Auto PBSCT after Ritux (33) Auto PBSCT after No Ritux (65) Chemo + Ritux (36) Chemo-only (112) (GELF-86 12.8 y GELF-94 7.6 y [ranges not stated])	Not Stated	(5-year EFS) 67% (a) 46% (b) 39% (c) 19% (d) a vs. b, *P* = .0532 c vs. d, *P* = .0002 a vs. c, *P* = .16 a + b vs. c + d, *P* < .0001 a + c vs. b + d, *P* < .0001	(5-year OS) 93% (a) 63% (b) 70% (c) 33% (d) a vs. b, *P* = .0071 c vs. d, *P* < .0001 a vs. c, *P* = .13 a + b vs. c + d, *P* < .0001 a + c vs. b + d, *P* < .0001	Not Stated

[17] Schouten et al. 2003 I− 1993-1997 EBMT CUP Multictr (36) Enrolled n = 140 Randomized n = 89 CUP analysis n = 70 Med Age (range): 48 y (29-64)	*Induction:* CHOP or other *Consolidation:* Chemo only (C) - CHOP *HDT:* Cy + f-TBI + Unpurged Auto BMT (U) or Purged Auto BMT (P)	FL 100% Relapses ≥2 35% IPI ≥3 28%	(ITT) (Chemo) C (24) (Unpurged Auto BMT) U (22) (Purged Auto BMT) P (24) (5.8 y [not stated])	(Not Stated) 0% 13.6% 8% (*P* not stated)	(2-year PFS) 26% CI 8%-44% 58% CI 37%-79% 55% CI 34%-75% (*P* = .0037)	(4-year OS) 46% CI 25%-67% 71% CI 52%-91% 77% CI 60%-95% (*P* = .079)	Not Stated
[18] Brice 2000 2++ 1986-1995 GELA Multictr (40) Retrospective analysis Eligible n = 372 Analyzed n = 364 Med Age (range): Auto SCT 45 y (17-57y) Non-SCT 58 y (24-77y)	Salvage varied by physician Auto SCT *HDT:* TBI 71% BEAM 29% Non-SCT Various chemo regimens	100% FL in 1st progression (HT 24%, 217 pts)	 Auto SCT (83) Non-SCT (281) (3.7 y [not stated])	(Not Stated) 6% 2% (*P* not stated)	Not Stated	(5-year OS) 58% ± 7.2% 38% ± 3.3% (*P* = .0002)	(Not stated) 5% 1% (*P* not stated)
[19] Rohatiner et al. 2007 2− 1985-1992 2 ctrs, Retrospective n = 155 Med Age (range): 43 y (24-61y) Med Chemo Reg (range): Not stated (2-≥3) Med Dx to SCT (range): 3.3 y (0.3-13.2 y)	Auto BMT *HDT:* Cy + TBI *Purging:* mAbs + Comp Non-SCT Chlorambucil or CVP	100% FL ≥CR2 100%	 Auto BMT (121) Non-SCT (34) (13.5 y [not stated])	Not Stated	Not Stated	(5-year OS) Survival estimates were not provided See Figure 5 Auto SCT versus Non-SCT (*P* = .02)	(Not Stated) 12% (deaths) Not Stated

aaIPI indicates Age-adjusted International Prognostic Index; APO, doxorubicin/vincristine/prednisone; Auto, autologous; BCNU, carmustine; BEAM, BCNU/etoposide/cytarabine/melphalan; BM(T), bone marrow (transplantation); CHOP(-R), cyclophosphamide/doxorubicin/vincristine/prednisone(+Rituximab); CHVP, cyclophosphamide/doxorubicin/vepeside/ prednisone; CI, 95% confidence interval; Comp, complement; Cy, cyclophosphamide; CR, complete remission; CVP, cyclophosphamide/vincristine/prednisone; Dex, dexamethasone; DFS, disease-free survival; DHAP, dexamethasone/cytarabine/cisplatin; Dx, diagnosis; DLBCL, diffuse large B cell lymphoma; EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; f-(TBI), fractionated (total body irradiation); GF, growth factor; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GITMO/IIL, Gruppo Italiano Trapianto di Midollo Osseo/Intergruppo Italiano Linfomi; GLSG, German Low Grade Lymphoma Study Group; GOELAMS, Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang; HD, High dose; HDT, High dose therapy; HT, Histologic transformation; ICE, Ifosfamide/carboplatin/etoposide; IFN-α , Interferon alfa; IMVP16, Ifosfamide/etoposide/methotrexate; IPI, International Prognostic Index; ITT, intention to treat; LPL, lymphoplasmacytic lymphoma; mAbs, monoclonal antibodies; MC, mantle cell lymphoma; MCP, Mitoxantrone/chlorambucil/ prednisone; MDS/AML, myelodysplastic syndromes/acute myelogenous leukemia; Mel, melphalan; MINE, mesna/ifosfamide/mitoxantrone/etoposide; Mito, mitoxantrone; OS, Overall survival; PB(SCT), peripheral blood (stem cell transplantation); PFS, progression-free survival; PR, partial remission; RFS, relapse-free survival; Ref, reference; Ritux, rituximab; SLL, small lymphocytic lymphoma; SCT, stem cell transplantation; TRM, treatment-related mortality; Tx, treatment; VCAP, vindesine/cyclophosphamide/ doxorubicin/prednisone; VP-16, etoposide.

*Quality and strength of evidence definitions are listed in Table 1.

†CVP and COP both consist of cyclophosphamide/vincristine/prednisone—the acronym CVP was used in this review.

irradiation (TBI), followed by autologous PBSCT. Three patients in the autologous PBSCT group and six in the IFN-α group were excluded from the analysis because of lack of diagnostic confirmation. Of the 431 evaluable patients, 236 received IFN-α maintenance and 195 received autologous PBSCT. Although randomized to the two study groups, the number of patients in the groups varied because some patients in the autologous PBSCT group did not have a sufficient stem cell collection to proceed or the patient refused PBSCT. Analyses were based on treatment received. Clinical characteristics of patients in the two study groups were comparable. The autologous PBSCT patients had a significantly higher 5-year PFS than patients in the IFN-α group. OS was not stated.

Studies of First-Line Autologous SCT versus Nontransplantation Therapy (without Rituximab)

Sebban et al. [11] reported the results of a prospective, multicenter study (GELF-94) by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) of 401 adult (median age, 49 years) patients with untreated advanced FL (96%) randomized to either CHOP induction therapy then high dose Cy + TBI + etoposide followed by autologous PBSCT (n = 192) or induction therapy consisting of Cy + doxorubicin + teniposide + prednisone (CHVP) followed by CHVP + IFN-α maintenance (n = 209). Patient clinical and biologic characteristics were similar, as were overall response rates (78% and 79%, respectively) in the autologous PBSCT and maintenance groups. Of the 150 eligible for autologous PBSCT, 131 underwent the procedure. Analyses were based on intention to treat. FL patients who underwent autologous SCT had a significantly higher 7-year EFS, but not OS, than those in the CHVP + IFN-α maintenance group. Figure 2 presents the probability of EFS for patients in the two treatment arms.

Lenz et al. [12] reported the outcomes of a subgroup of 240 adult (26-59 years) patients with FL in first remission enrolled in a prospective, multicenter GLSG study of 375 lymphoma patients. After induction therapy with CHOP or mitoxantrone + chlorambucil + prednisone (MCP), patients were randomized to receive either high-dose therapy with Cy + TBI followed by an autologous PBSCT (n = 114) or IFN-α maintenance therapy (n = 126). In the autologous PBSCT group, 19.3% and 80.7% of patients achieved CR and PR, respectively. In the IFN-α group, 15.9% and 84.1% achieved CR and PR, respectively. Analyses were based on treatment received. The characteristics of patients in the two groups were comparable. Autologous PBSCT patients had a significantly higher 5-year PFS than IFN-α maintenance patients. OS was not stated. Figure 3 presents the probability of PFS after autologous PBSCT or IFN-α maintenance.

Gyan et al. [13] presented the long-term results of a prospective, multicenter study by the Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) [14] of 166 adult (18-60 years) patients with untreated advanced FL who were randomized to either high dose therapy followed by *in vivo* purged autologous SCT (n = 86) or to standard chemotherapy + IFN-α maintenance (n = 80). There were more women, more patients with B symptoms, and fewer patients with Grade 3 follicular histology in the maintenance group than in the autologous SCT group. Ninety percent of autologous SCT, and 77% of standard chemotherapy patients completed the assigned treatment. Analyses were based on intention to treat. Autologous SCT patients had a significantly higher 9-year EFS, but not OS, than IFN-α maintenance patients.

Horning et al. [15] reported the results of 37 adult (26-49 years) patients with advanced stage, previously untreated FL enrolled in a nonrandomized prospective trial of high-dose therapy consisting of Cy + vincristine + prednisone (CVP) followed by *ex vivo* purged autologous bone marrow transplant (BMT). A reference sample of 188 patients of similar age, stage, and histology who received conventional chemotherapy (no details were reported) was identified for comparison of patient outcomes. Five-year OS estimates for both groups were provided, but not compared.

Salvage Autologous SCT versus Nontransplantation Therapy ± Rituximab

Four studies examined autologous SCT versus chemotherapy as salvage therapy for patients with relapsed/progressed FL. One study investigated autologous PBSCT after chemotherapy ± rituximab, whereas the other three studies did not use rituximab in their protocols. The quality of these studies ranged from 1− to 2−. The study comparing autologous PBSCT versus chemotherapy ± rituximab found that patients in first relapse who underwent autologous SCT after salvage including rituximab had improved 5-year OS and EFS after relapse than patients who received rituximab-based salvage therapy without an autologous SCT. Of the three studies without rituximab, one study reported significantly better 2-year PFS, and two studies reported superior 5-year OS for patients who underwent salvage autologous SCT versus chemotherapy.

Study of Salvage Autologous SCT versus Nontransplantation Therapy (± Rituximab)

Sebban et al. [16] performed a retrospective analysis of a subgroup of 246 adult (18-70 years) patients

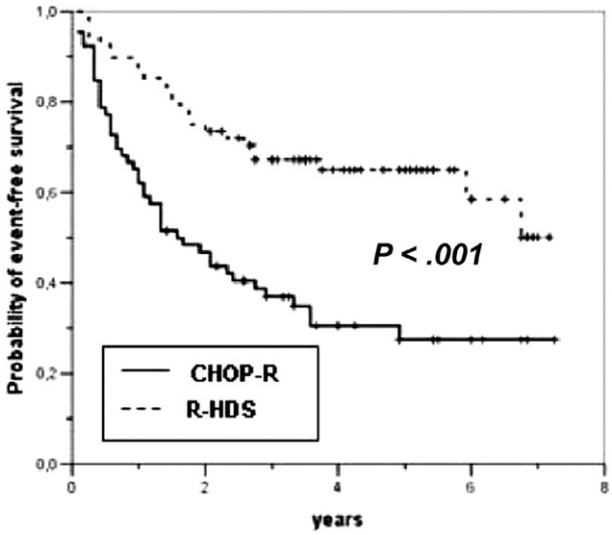

Figure 1. The probability of EFS for patients in the two treatment arms. (This research was originally published in *Blood,* Ladetto et al., 2008 [9]. Reprinted with permission. © 2008 the American Society of Hematology. All rights reserved.)

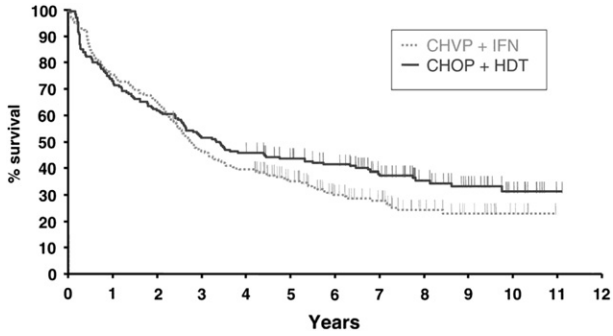

Figure 2. The probability of EFS for patients in the two treatment arms. (This research was originally published in *Blood,* Sebban et al., 2006 [11]. Reprinted with permission. © 2006 the American Society of Hematology. All rights reserved.)

who relapsed or had disease progression after initial treatment in the GELA GELF-94 and GELF-86 prospective, randomized studies, which are described in this review [11,18]. Patients were compared according to salvage treatment, as follows: chemotherapy alone (n = 112), chemotherapy + rituximab (n = 36), chemotherapy + rituximab + autologous SCT (n = 33), or chemotherapy + *no* rituximab + autologous SCT (n = 65). Patients treated with rituximab had higher Follicular Lymphoma International Prognostic Index (FLIPI) scores and a lower occurrence of B symptoms at diagnosis, and patients who underwent autologous SCT were younger and more likely to have relapsed than progressive disease. OS was highest in patients who underwent rituximab-based salvage + autologous SCT, followed by rituximab-based salvage without SCT, salvage with no rituximab + autologous SCT, and salvage chemotherapy without rituximab or SCT.

Studies of Salvage Autologous SCT versus Nontransplantation Therapy (without Rituximab)

Schouten et al. [17] reported the results of 140 adult (29-64 years) patients with relapsed FL enrolled in the prospective, multicenter European Group for Blood and Marrow Transplantation (EBMT) CUP trial, which compared the effectiveness of standard therapy (C) versus high-dose therapy followed by unpurged (U) or *ex vivo* purged (P) autologous SCT. It should be noted that recruitment to this trial was discontinued because of slow accrual once the sample size required for the C and P comparison was achieved. The accrual rate was considerably lower than that required to examine other comparisons adequately. Of the 140 patients enrolled, 89 patients were randomized, 70 among three treatment arms (C, U, and P), and 19 to only the U and P arms. Reasons for not randomizing included patient refusal, early progression, or death after induction therapy. Salvage therapy was three cycles of CHOP or another regimen. Patients in the C arm received three additional cycles of CHOP as consolidation therapy. High-dose therapy for patients in the U and P arms consisted of Cy + fractionated TBI (f-TBI), followed by unpurged or purged autologous SCT, respectively. Of the 70 patients in the three treatment arms, 88% of the C group, 85% of the U group, and 67% of the P group received the assigned treatment. Analyses were based on intention to treat. Both the purged and unpurged autologous SCT groups had a significantly higher 2-year PFS, but not OS, than the chemotherapy-only group. Figure 4

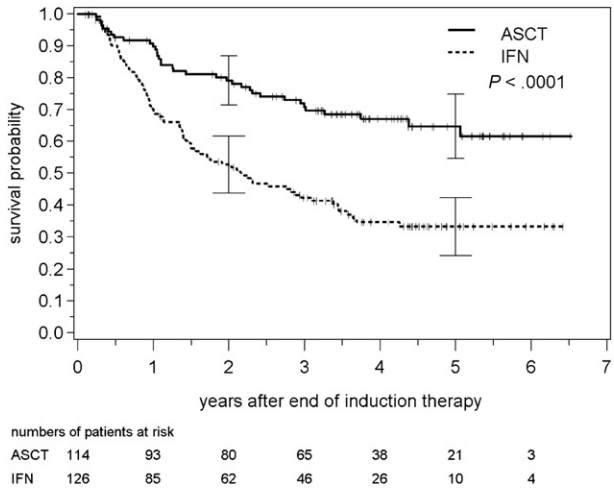

Figure 3. PFS after high-dose radiochemotherapy followed by ASCT or IFN-α maintenance in follicular lymphoma. (This research was originally published in *Blood,* Lenz et al., 2004 [12]. Reprinted with permission. © 2004 the American Society of Hematology. All rights reserved.)

presents the probability of PFS for patients in the three treatment arms.

Brice et al. [18] reported the results of a retrospective analysis of 372 adult (17-57 years) patients with FL who experienced progressive/relapsing disease after standard chemotherapy in a prospective GELA study (GELF-86). The median time from initial treatment to first progression was 24 months. Of the 372 patients, 281 (75%) received standard chemotherapy for first progression, and 91 (25%) patients received salvage therapy consisting of a TBI-containing regimen (71%) or carmustine + etoposide + cytarabine + melphalan (BEAM) followed by autologous (n = 83) or allogeneic (n = 8) SCT. Allogeneic SCT patients were excluded from the analysis. Stem cell source was peripheral blood (73%) or marrow. Response rates were 88% and 54% in the autologous SCT versus standard chemotherapy patients, respectively. Autologous SCT patients had a significantly higher 5-year OS than chemotherapy-only patients.

Rohatiner et al. [19] presented the results of a retrospective analysis of 121 adult (24-61 years) patients with FL who received salvage therapy at the time of second or subsequent remission consisting of high-dose Cy + TBI followed by *ex vivo* purged autologous BMT. Long-term survival outcomes were compared to a historical control group of 34 age-matched, remission-matched patients who received either chlorambucil or CVP as initial and salvage therapy. Actual OS estimates were not provided; however, Figure 5 compares OS by treatment received and shows that the Cy + TBI + autologous BMT patients had a significantly higher OS than the control group.

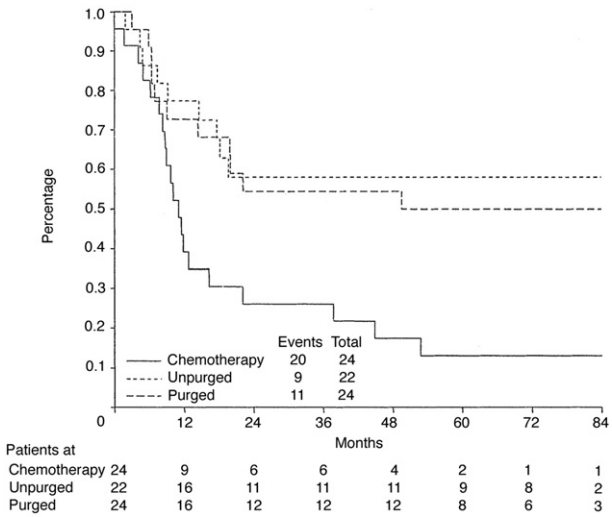

Figure 4. The probability of PFS for patients in the three treatment arms. (Schouten et al., 2003 [17]. Reprinted with permission. © 2003 American Society of Clinical Oncology. All rights reserved.)

AUTOLOGOUS VERSUS ALLOGENEIC SCT

Presented in this section are five studies that compared the outcomes of autologous versus myeloablative (MA) allogeneic SCT as treatment for refractory or relapsed FL. The quality of these cohort studies ranged from 2+ to 2−. Table 5 presents a summary of the design, methodology, and outcomes data from these studies.

In all five studies, allogeneic SCT had a significantly higher treatment-related mortality (TRM) and lower relapse rate compared to autologous SCT. Few studies reported a significant difference in survival outcomes between autologous and allogeneic SCT. One study reported significantly better 5-year OS for patients who underwent autologous SCT compared to allogeneic SCT. Two studies reported significantly improved disease-free survival (DFS) for allogeneic compared to unpurged autologous SCT patients.

Studies of Autologous SCT versus Allogeneic SCT

van Besien et al. [20] reported the results of 904 adult (18-71 years) patients with early (CR1, CR2, or first relapse) or advanced (>CR2, equal to or greater than second relapse, or primary induction failure) follicular lymphoma who underwent unpurged (n = 597) or purged (n = 131) autologous SCT, or human leukocyte antigen (HLA)-identical sibling allogeneic SCT (n = 176), and were reported to the International Bone Marrow Transplant Registry (IBMTR) or the Autologous Blood and Marrow Transplant Registry (ABMTR). Time from diagnosis to transplantation was less than 1 year (19%), 1-2 years (27%), or more than 2 years (54%). Allogeneic SCT patients had

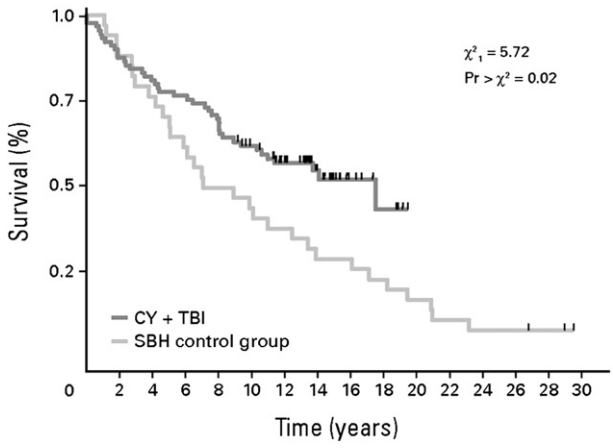

Figure 5. Comparison of overall survival between patients treated with Cy+TBI and control group. (Rohatiner et al., 2007 [19]. Reprinted with permission. © 2007 American Society of Clinical Oncology. All rights reserved.)

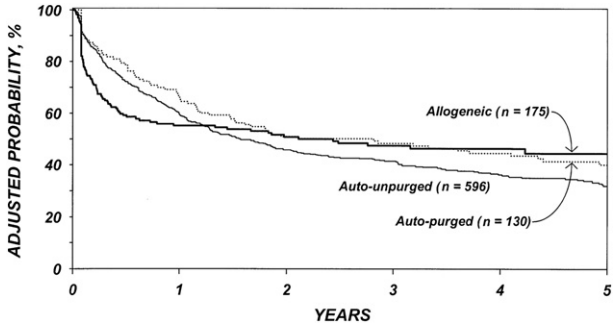

Figure 6. Probabilities of disease-free survival by type of transplant, adjusted for significant covariates. ((This research was originally published in *Blood,* van Besien et al., 2003 [20]. Reprinted with permission. © 2003 the American Society of Hematology. All rights reserved.)

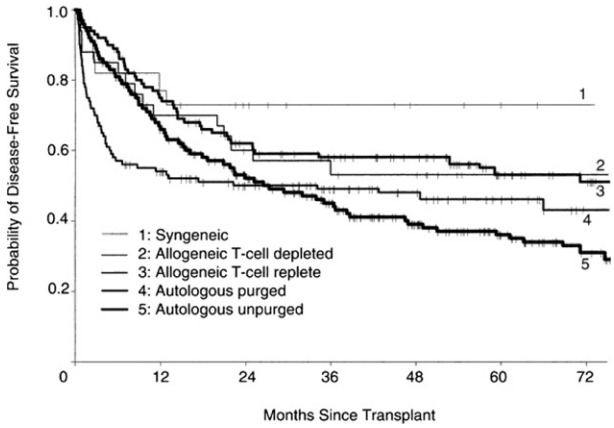

Figure 7. Actuarial probability of DFS for low-grade lymphoma patients according to type of transplant. (Bierman et al., 2003 [21]. Reprinted with permission. © 2003 American Society of Clinical Oncology. All rights reserved.)

a significantly higher 5-year DFS than patients who underwent unpurged autologous SCT. There was no significant difference in 5-year DFS between allogeneic and purged autologous SCT patients, or among any groups in 5-year OS. Figure 6 presents the probability of DFS by type of transplantation, adjusted for significant covariates.

Bierman et al. [21] presented the results of 3376 NHL patients (median age, 42 years), of whom 842 (25%) were low-grade NHL. Outcomes of low-grade NHL patients from the EBMTR and IBMTR who underwent syngeneic SCT (n = 30) were compared to patients from the IBMTR/ABMTR who underwent high-dose therapy followed by unpurged (n = 427) or purged (n = 160) autologous SCT or T cell-replete (n = 189) or T cell-depleted (n = 36) allogeneic SCT. Nonmyeloablative allogeneic SCT patients were excluded. Allogeneic SCT patients were younger and more likely to have a history of BM involvement and high-grade histology than autologous SCT patients. When compared with syngeneic SCT, unpurged autologous SCT for low-grade NHL had a significantly higher risk of relapse (RR, 4.93; P = .008), and DFS was significantly worse for T cell-replete allogeneic SCT (RR, 3.12; P = .006) and unpurged autologous SCT (RR, 2.28; P = .04) recipients. There were no significant differences in relapse risk among syngeneic SCT, purged autologous SCT, and T cell-replete or T cell-depleted allogeneic SCT recipients. Low-grade NHL patients who received T cell-replete allogeneic SCT also had significantly worse OS than syngeneic SCT patients (RR, 2.87; P = .006). There were no significant differences in OS between autologous and syngeneic SCT. Unpurged autologous SCT was associated with poorer OS, when compared to purged autologous SCT (RR, 1.55; P = .04). Figure 7 presents the probability of DFS for low-grade lymphoma patients according to type of transplantation.

Hosing et al. [22] reported the results of 112 adult (23-69 years) patients with refractory or relapsed NHL (86% follicular) who underwent either autologous (n = 68) or allogeneic (n = 44) SCT. The 2 groups were comparable with respect to age at SCT, sex, histologic subtypes, and median number of chemotherapy regimens before SCT. Donors for allogeneic SCT were HLA-matched sibling (89%), 1-antigen HLA-mismatched related (7%), or HLA-matched unrelated (5%). There was no significant difference in DFS or OS between allogeneic and autologous SCT patients.

Stein et al. [23] presented the results of 51 adult (29-63 years) patients with relapsed or refractory small cleaved cell lymphoma who underwent autologous (n = 36) or allogeneic (n = 15) SCT after high dose chemotherapy ± TBI. Allogeneic SCT patients were significantly younger and had a higher incidence of BM involvement than autologous SCT patients. Autologous SCT patients had a significantly higher 5-year OS, but not PFS, than allogeneic SCT patients.

Ingram et al. [24] reported the results of 126 adult (30-74 years) patients with relapsed, advanced stage FL who underwent BEAM and autologous (n = 82) or allogeneic SCT (n = 44). Donors for allogeneic SCT were HLA-matched (64%) or ≥1 antigen HLA-mismatched (2%) sibling, or HLA-matched (20%) or HLA-mismatched (14%) unrelated. The allogeneic group had a significantly younger median age than the autologous SCT group. There was no significant difference in 3-year DFS or OS between allogeneic and autologous SCT patients.

AUTOLOGOUS SCT

The autologous SCT section is composed of nonrandomized comparative and noncomparative

Table 5. Patient Characteristics and Outcomes from Autologous SCT versus Allogeneic SCT Studies

Study Design			Patient Outcomes				
(Ref #), Qual. and Strength of Evidence,* and Patient Population	Protocols	Diagnosis or FL Subtype (at Dx unless Stated)	Study Groups (n) (Med Follow-up [Range])	(Interval) % TRM (Significance)	(Interval) % Relapse (Significance)	(Interval) % DFS/RFS/ PFS/EFS (Significance)	(Interval) % OS (Significance)
[20] van Besien et al. 2003 2+ 1990-1999 IBMTR/ABMTR Multictr (175) Registered n = 2459 Included n = 904 Med Age (range): Auto SCT 49 y (18-71 y) Allo SCT 42 y (22-64 y)	*Induction:* CHOP ± other or Flu ± other Auto SCT *Purging:* 4-HC *HDT*: Mostly chemo Allo SCT *y Conditioning:* Mostly TBI	FL 100% Stage ≥III 80% Status at SCT Early 56% Advanced 44%		(5-yr TRM)	(5-yr Relapse)	(5-year DFS)	(5-year OS)
			Unpurged Auto (597) (3.4 y [not stated])	8% CI 6%-11%	58% CI 53%-63%	31% CI 27%-36%	55% CI 50%-60%
			Purged Auto (131) (4.1 y [not stated])	14% CI 8%-22%	43% CI 35%-54%	39% CI 30%-48%	62% CI 53%-72%
			Allo SCT (176) (3 y [not stated])	30% CI 23%-40%	21% CI 15%-28%	45% CI 36%-53%	51% CI 43%-60%
				Allo vs Auto ($P < .05$)	Allo vs Auto ($P < .05$)	Allo vs Unpurged Auto ($P = .05$) Allo versus Purged Auto (P not significant)	(P not significant)
[21] Bierman et al. 2003 2+ 1985-1998 EBMT/IBMTR/ABMTR Multictr (1286) Total n = 3376 LGNHL n = 842 (Stratified) (All patients) Med Age (range): Syngeneic 42 y (4-68 y) Auto SCT 48 y (6-71 y) Allo SCT 35 y (2-62 y)	*Purging Methods:* 4-HC or Mafosfamide 57% Pos Selection tech 12% mAbs 8% Other agents 23% *TBI for HDT/Conditioning:* Syngeneic 28% Unpurged Auto 28% Purged Auto 60% Replete Allo 72% Depleted Allo 90% GF Post-SCT 47%	LG NHL 25% IG NHL 55% HG NHL 20% Status at SCT Refractory 22% CR1 15% ≥CR2 17% Relapse 1 28% Relapse 2 8% Unknown 10%	(LG NHL Only) Syngeneic (30) (3.7 y [0.3-15.5 y]) Unpurged Auto (427) (3 y [< 0.8-10.4 y]) Purged Auto (160) (3.8 y [0.3-10.7 y]) T cell-replete Allo(189) (4 y [0.2-14.5 y]) T cell-depleted Allo (36) (5 y [0.3-13.3 y])	Not Stated	*See text for RR estimates of Relapse for LG NHL*	*See text for RR estimates of DFS for LG NHL*	*See text for RR estimates of OS for LG NHL*
[22] Hosing et al. 2003 2+ 1991-2000 Single Ctr n = 112 (All patients) Med Age (range):	*Induction:* Flu 35% Auto 57% Allo Ritux 2% Auto 9% Allo Auto SCT *Purging*: mAbs 82%	FL 86% SLL 14% Ref/Rel 100% Status at SCT Auto SCT CR 26%		(100 day)	(Not stated)	(Not stated, DFS)	(Not stated, OS)
			Auto SCT (68) (5.9 y [1.8-9.1 y])	6%	74% CI 59%-88%	17% CI 8%-30%	34% CI 17%-53%
			Allo SCT (44) (4.4 y [1.8 -9.4 y])	34%	19% CI 9%-38%	45% CI 30%-59%	49% CI 33%-63%

Auto SCT 42 y (24-59 y) Allo SCT 43 y (23-61 y) Med Chemo Reg (range): Auto SCT 2 (1-9) Allo SCT 3 (1-6) Med Dx to SCT (range): Auto SCT 3.8 y (0.9 – 15.9 y) Allo SCT 2.3 y (0.3 – 22.8 y) ($P = .002$)	*HDT:* Cy + VP-16 + TBI Allo SCT *SC Mobil*: GF *Conditioning*: Cy + VP-16 + TBI 55% or BEAM 45%	PR 74% Allo SCT CR 2% PR 98%		($P < .001$)	($P = .003$)	(P not significant)	(P not significant)
[23] Stein et al. 1999 2+ 1985-1996 Single Ctr n = 51 Med Age (range): Auto SCT 48 y (29-63 y) Allo SCT 43 y (31-50 y) Med Chemo Reg (range): Auto SCT 2.5 (1-6) Allo SCT 2 (1-4) Med Dx to SCT (range): Auto SCT 3 y (0.5 – 16 y) Allo SCT 2.5 y (0.6 – 8.9 y)	Auto SCT *Purging:* VP-16 + Methylprednisolone 86% *HDT:* Cy + VP-16 + f-TBI or CBV Allo SCT *Conditioning*: CBV or Cy + VP-16 + f-TBI	SCCL 100% Ref/Rel 100% ≥Stage III 100%	Auto SCT (36) Allo SCT (15) [Not Stated]	(Not stated) 14% 53% (P not stated)	Not Stated	(5-year PFS) 71% ± 9% 64% ± 15% ($P = .49$)	(5-year OS) 56% ± 11% 15% ± 13% ($P = .012$)
[24] Ingram et al. 2008 2− 1992-2005 2 Ctrs n = 126 Med Age (range): Auto SCT 56 y (30-74 y) Allo SCT 48 y (31-59 y) Med Chemo Reg (range): Auto SCT 2 (1-6) Allo SCT 3 (1-8) Med Dx to SCT (range): Auto SCT 2.1 y (0.4-10 y) Allo SCT 2.8 y (0.5-31 y)	Auto SCT *PBSC Mobil*: Chemo + GF *HDT:* BEAM Allo SCT *PBSC Mobil:* GF *Conditioning:* BEAM + Alemtuzumab	FL 100% Relapsed 100% ≥Stage III 100%	Auto SCT (82) (7.3 y [0.92-13.9 y]) Allo SCT (44) (2.9 y [0.55-8.3 y])	(1-year) 2% 20% ($P = .001$)	(3-year) 43% 20% ($P = .01$)	(3-year DFS) 56% 58% ($P = .90$)	(3-year OS) 67% 69% ($P = .99$)

4-HC indicates 4-hydroxyperoxycyclophosphamide; ABMTR, Autologous Blood and Marrow Transplant Registry; Allo, Allogeneic; Auto, autologous; BEAM, BCNU/cytarabine/etoposide/ melphalan; BM(T), bone marrow (transplantation); CBV, cyclophosphamide/BCNU/etoposide; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, 95% confidence interval; CR, complete remission; Cy, cyclophosphamide; DFS, disease-free survival; Dx, diagnosis; EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; FL, follicular lymphoma; Flu, fludarabine; GF, growth factor; HD, high dose; HDT, High-dose therapy; HG, high grade; IBMTR, International Bone Marrow Transplant Registry; IG, intermediate grade; LG, low grade; mAbs, monoclonal antibodies; NHL, non-Hodgkin lymphoma; OS, overall survival; PB(SC), peripheral blood (stem cell); PFS, progression-free survival; PR, partial remission; RFS, relapse-free survival; Ref, reference; Ritux, rituximab; SCCL, small cleaved cell lymphoma; SLL, small lymphocytic lymphoma; SCT, stem cell transplantation; TBI, total body irradiation; TRM, treatment-related mortality; VP-16, etoposide.
*Quality and strength of evidence definitions are listed in Table 1.

studies. Eight nonrandomized comparative studies of autologous SCT in the treatment of follicular lymphoma are summarized in the next section, including one study that investigated the impact of first-line versus salvage autologous SCT (timing of transplantation), three studies that investigated rituximab versus no rituximab prior to autologous SCT, one study of purged versus unpurged autologous BMT, and three studies that compared high-dose therapy regimens for autologous SCT. All but one of these studies have a 2+ quality rating, the exception has a 2− rating. Table 6 presents a summary of the design and outcomes data from the comparative autologous SCT studies.

In addition, there are 29 noncomparative, single cohort studies included in this review that examined the use of autologous SCT as primarily first-line (10 studies) or salvage (13 studies) treatment for FL. Also included are six noncomparative studies of the effectiveness of autologous SCT with >20% histologically transformed FL patients. The quality of the noncomparative cohort studies ranged from 2++ to 2+. These studies represent nonrandomized single- or multi-institutional experiences with autologous SCT or retrospective analyses of transplantation registry data. Collectively, the outcomes data from these studies contribute to the overall understanding of the effectiveness of autologous SCT in the treatment of FL. The design, methodology, and outcomes data from these studies are summarized in Appendix Table 1 (available online only).

Comparative Studies of Autologous SCT

First-line versus Salvage Autologous SCT (Timing of Transplantation)

One cohort study of the impact of timing of transplantation on FL outcomes examined autologous SCT as first-line versus salvage therapy. Seyfarth et al. [25] reported a retrospective analysis of 55 adult (26-60 years) patients with advanced-stage FL who underwent autologous SCT as first-line (n = 33) or salvage (n = 22) treatment at a single center. Significantly more first-line patients received TBI therapy and were in CR or PR at time of mobilization, whereas more salvage patients had untreated relapsed disease. Four-year EFS and OS were significantly different in patients undergoing autologous SCT as first-line therapy versus as salvage therapy.

Rituximab versus no Rituximab Prior to Autologous SCT

The following three cohort studies examined the impact of rituximab as part of induction or salvage therapy prior to SCT on FL or low-grade NHL patient outcomes. Two studies found no significant differences in survival outcomes, whereas one study reported a significantly improved 5-year EFS and OS in patients who received pre-SCT rituximab.

Tarella et al. [26] presented a retrospective analysis of a Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) study that treated 745 adult (17-65 years) patients with high-risk FL (n = 223, 30%) or diffuse large B cell lymphoma (n = 522, 70%), comparing the outcomes of those who received rituximab prior to first-line or salvage autologous PBSCT versus those who did not. Patient outcomes were stratified by lymphoma histology. Of the FL patients, 116 (52%) received rituximab whereas 107 did not, and 94 (42%) underwent PBSCT as first-line versus 129 as salvage therapy. Five-year EFS and OS were significantly higher in FL patients receiving pre-SCT rituximab versus no rituximab. Figure 8A and B presents estimated EFS for patients who underwent PBSCT as first-line or salvage therapy, with (R+) or without (R−) rituximab.

Hoerr et al. [27] presented the results of a retrospective analysis of 265 adult (23-73 years) patients with relapsed low-grade (n = 111, 42%) or intermediate-grade (n = 154) NHL, comparing the outcomes of those who received rituximab versus those who did not as part of induction or salvage therapy prior to autologous SCT. Patients who received rituximab as part of stem-cell mobilization, high-dose therapy regimen, or post-SCT maintenance were excluded. Of the low-grade patients, 56 (50%) received rituximab, and 55 did not. There was no significant difference in 3-year DFS or OS between pre-SCT rituximab versus no rituximab low-grade NHL patients. Figure 9 presents the probability of DFS in low-grade lymphoma patients by pre-SCT rituximab (R group) versus no rituximab (NR group).

Kang et al. [28] reported the results of a retrospective analysis of 125 adult (mean age 50 years) patients with FL who underwent autologous PBSCT. Of the 125, 19 patients who received rituximab as part of salvage therapy prior to SCT were excluded. Of the remaining 106 patients, 35 (33%) received pre-PBSCT rituximab and 71 did not. There was no significant difference in median relapse free survival (RFS) between pre-PBSCT rituximab versus no rituximab patients.

Purged versus Unpurged Autologous BMT

The randomized CUP trial [18], which examined the impact of purging in autologous SCT, was previously described in the Salvage Autologous SCT versus Nontransplantation Therapy section. In addition, the following cohort study examined the impact of purged versus unpurged autologous BMT on low-grade lymphoma patient outcomes.

Williams et al. [29] reported the results of an EBMTR study of 50 adult (17-62 years) low-grade NHL patients who underwent purged autologous

Table 6. Patient Characteristics and Outcomes from Comparative Autologous SCT Studies

Study Design			Patient Outcomes				
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocols	Diagnosis or FL Subtype (at Dx unless Stated)	Study Groups (n) (Med Follow-up [range])	(Interval) % TRM (Significance)	(Interval) % DFS/RFS/PFS/EFS (Significance)	(Interval) % OS (Significance)	(Interval) % MDS/AML (Significance)
FIRST-LINE VERSUS SALVAGE AUTOLOGOUS SCT (TIMING OF TRANSPLANTATION)							
[25] Seyfarth et al. 2001 2− 1992-1999 Single Center n = 55 Med Age (range): 45 y (26-60 y) Med Chemo Reg (range): 1 (1-4) Med Dx to SCT (range): 0.9 y (0.4-14 y)	*Induction*: CHOP, CHOEP, CVP, MCP, PmM, or other ± RT *SC Mobil:* Chemo *HDT:* Cy + f-TBI 58% Bu + Cy 26% BEAM 16% No exposure to mAbs	FL 100% ≥Stage III 100% First-line CR1 or PR1 85% Salvage Untreated Rel 77%	 First-line Auto SCT (33) Salvage Auto SCT (22) (4 y (0.8-7.5 y])	(4-year TRM) (Overall) 2%	(4-year EFS) 76% 38% (*P* < .02)	(4-year OS) 92% 73% (*P* = .033)	(4-year) 0% 0%
PRE-SCT RITUXIMAB VERSUS NO RITUXIMAB							
[26] Tarella et al. 2008 2+ 1986-2005 GITIL Multictr (10) n = 745 FL n = 223 (Stratified) (All patients) Med Age (range): 47 y (17-65 y)	*HDS:* CHOP ± DHAP ± Ara-C *PBSC Mobil:* Chemo ± Ritux *HDT:* Mito + Mel or BEAM or other Ritux Post-Auto PBSCT	FL 30% DLBCL 70% (FL only) First-line 42% Salvage 58%	 (FL only) Ritux Auto PBSCT(116) No Ritux Auto PBSCT (107) (5 y [not stated])	(Not Stated for FL pts. only)	(5-year EFS) 66% 46% (*P* < .001)	(5-year OS) 82% 68% (*P* < .011)	Not Stated
[27] Hoerr et al. 2004 2+ 1996-2002 Single Ctr n = 273 LG NHL n = 111 (Stratified) (All patients) Med Age (range): Ritux 58 y (33-73 y) No Ritux 50 y (23-69 y) (LG NHL only) Mean Chemo Cycles (range): Ritux 14 (not stated) No Ritux 11 (not stated) Mean Dx to SCT (range): Ritux 4.3 y (not stated) No Ritux 3.3 y (not stated)	*Salvage Therapy:* ESHAP, DHAP, MINE, or ICE ± Ritux *SC Mobil:* GF *HDT*: f-TBI 41% BEAM 34% BEAC 25% GF Post-Auto SCT	LG NHL 42% IG NHL 58% Relapsed 100%	 (LG NHL only) Ritux Auto SCT (56) [1.5 y (not stated)] No Ritux Auto SCT (55) (1.8 y [not stated])	Not Stated	(3-year DFS) 53% 48% (*P* = .46)	(3-year OS) 73% 60% (*P* = .21)	Not Stated

(*Continued*)

Table 6. (*Continued*)

Study Design				Patient Outcomes			
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocols	Diagnosis or FL Subtype (at Dx unless Stated)	Study Groups (n) (Med Follow-up [range])	(Interval) % TRM (Significance)	(Interval) % DFS/RFS/PFS/EFS (Significance)	(Interval) % OS (Significance)	(Interval) % MDS/AML (Significance)
[28] Kang et al. 2007 2+ 1994-2004 Single Center n = 106 Ritux Mean Age: 55 ± 10 y No Ritux Mean Age: 50 ± 9 y (Age ranges not stated) Med Chemo Reg (range): Ritux 2 (1-7) No Ritux 2 (1-6) Med Dx to SCT (range): Ritux 2.3 y (0.7-15.3 y) No Ritux 2.1 y (0.3-17.6 y)	*Induction:* Unspecified chemo *PBSC Mobil:* GF ± chemo *HDT:* Cy + BU + VP-16 No maintenance Ritux	FL 100% IPI at PBSCT Ritux ≥3 17% No Ritux ≥3 33%	Ritux Auto PBSCT (35) (1.9 y [0.7 -5.2 y]) No Ritux Auto PBSCT (71) (6.5 y (1.3-10.7 y])	Not Stated	(Median RFS) 24.6 months 49.9 months (*P* = .47)	Not Stated	Not Stated
PURGED VERSUS UNPURGED AUTOLOGOUS BMT							
[29] Williams et al. 1996 2+ Not stated—1994 EBMTR Multictr (26) Total n = 448 LG NHL n = 100 (Stratified) (LG NHL) Med Age (range): Purged 44 y (25-58 y) Unpurged 45 y (17-62 y) Med Dx to BMT (range): Purged 1.1 y (0.3-7.8 y) Unpurged 2.3 y (0.1-22 y)	*Induction:* BEAM ± TBI (LG NHL only) *Purging:* Chemical 62% mAbs 30% CD34+ cell select 8% *HDT*: Chemo 57% Chemo + TBI 43%	LG NHL 22% IG NHL 20% Burkitt 18% LL 26% HG NHL 14% (LG NHL) Status at BMT CR1 26% CR2/3 26% VGPR 34% Refractory 2% Relapsed 12%	(LG NHL) Purged Auto BMT (50) (2.5 y [1.7-7.3 y]) Unpurged Auto BMT (50) (2.9 y [0.1-10.9 y])	(5-year TRM) 10% 16% (*P* not stated)	(5-year PFS) 48.4% 44.2% (*P* = .1757)	(5-year OS) 83.9% 47.6% (*P* = .0184)	Not Stated
COMPARISON OF HIGH-DOSE THERAPIES PRIOR TO AUTOLOGOUS SCT							
[30] Gopal et al. 2003 2+ 1990-1998 Single Ctr n = 125	*Prior RT:* HD-RIT 7% C-HDT 19% HD-RIT *HDT:* ^{131}I-Tositumomab+RT C-HDT	FL 100% Ref/Rel 100% *HT:* HD-RIT 15% C-HDT 8%	HD-RIT + Auto (27) C-HDT + Auto (98)	(100-day TRM) 3.7% 11%	(5-year PFS) 48% 29%	(5-year OS) 67% 53%	Estimated 8% @ 8 yrs 9% @ 7 yrs

Med Age (range): HD-RIT 46 y (24-59 y) C-HDT 49 y (30-59 y) Med Chemo Reg (range): HD-RIT 2 (1-6) C-HDT 2 (1-11)	*HDT:* Cy+VP-16+TBI 59% Cy+TBI 11% Bu+Mel+TT 21% Other combo 9%	 Status at SCT HD-RIT CR/PR 59% Ref/Rel 41% C-HDT CR/PR 68% Ref/Rel 32%	(Not Stated)	(*P* = .10)	(*P* = .06)	(*P* = .02)	(*P* not stated)
[31] Gutierrez-Delgado et al. 2001 2+ 1990-1998 Single Ctr Total n = 351 LG NHL n = 106 (Stratified) (All patients) Med Age (range): TBI+Cy+VP-16 47 y (18-65 y) Bu+Mel+TT 48 y (19-67 y) Med Chemo Reg (range): 2 (1-7)	*Prior RT:* TBI+Cy+VP-16 0% Bu+Mel+TT 45% *BM Purging:* Anti-B mAbs 19% Anti-T mAbs 3% *PBSC Mobil:* GF alone 26% Chemo + GF 58% *RT Post-Auto SCT:* TBI+Cy+VP-16 5% Bu+Mel+TT 8%	LG NHL 35% Aggress NHL 63% SLL 2% Status at SCT TBI+Cy+VP-16 CR1 4% ≥CR2 15% Ref/Rel 81% Bu+Mel+TT CR1 5% ≥ CR2 19% Ref/Rel 76%	(LG NHL) TBI+Cy+VP-16+Auto (76) (5 y [1-9 y]) Bu+Mel+TT+Auto (30) (3.5 y [1-6 y])	(Not stated) 13% 17% (*P* = .80)	(5-year EFS) 37% 36% (*P* not significant)	Not Stated for LG NHL Only	(4-year) 3% 0% (*P* not stated)
[32] Weaver et al. 1998 2+ 1991-1995 Multictr (19) n = 49 (All patients) Med Age (range): Bu+Cy 46 y (25-62 y) BEAC 53 y (22-64 y) Med Chemo Reg (range): Not stated (1- ≥3)	*Prior RT:* Bu + Cy 41% BEAC 30% *PBSC Mobil*: Chemo + GF *HDT:* Bu + Cy 45% BEAC 55% GF Post-PBSCT 80%	FL 82% SLL 18% Status at SCT Bu+Cy Refractory 50% Relapsed 50% BEAC Refractory 33% Relapsed 67%	Bu + Cy +Auto PBSCT (22) BEAC + Auto PBSCT (27) (3.6 yrs [not stated])	(3.6-yr TRM) 9% 7% (*P* not stated)	(3.6-yr EFS) 36% 28% (*P* = .82)	(3.6-yr OS) 58% 55% (*P* = .72)	Not Stated

Auto indicates autologous; BCNU, carmustine; BEAC, carmustine/etoposide/cytarabine/cyclophosphamide; BEAM, carmustine/etoposide/cytarabine/melphalan; BEM, carmustine/etoposide/melphalan; BM(T), bone marrow (transplantation), Bu, Busulfan; CBV, cyclophosphamide/carmustine/etoposide; C-HDT, Conventional high dose therapy + Auto SCT Chemo, Chemotherapy; CHOEP, Cyclophosphamide/doxorubicin/etoposide/prednisone; CHOP(-R), cyclophosphamide/doxorubicin/vincristine/prednisone(+Rituximab); CI, 95% Confidence interval; CR, Complete remission; CVP, cyclophosphamide/ vincristine/prednisone; Cy, cyclophosphamide; DFS, disease-free survival; DHAP, dexamethasone/cytarabine/cisplatin; DLCL, Diffuse large cell lymphoma; Dx, diagnosis; EBMTR, European Group for Blood and Marrow Transplantation Registry; EFS, event-free survival; ESHAP, etoposide/solumedrol/cytarabine/platinum; FL, Follicular lymphoma; Flu, fludarabine; f-TBI, fractionated total-body irradiation; GF, growth factor; GITIL, Gruppo Italiano Terapie Innnovative nei Linfomi; HD, High dose; HD-RIT, high-dose radioimmunotherapy + Auto SCT; HDT, high-dose therapy; HG, high grade; HT, histologic transformation; ICE, ifosfamide/carboplatin/etoposide; IG, intermediate grade; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LG, low grade; LL, lymphoblastic leukemia; mAbs, monoclonal antibodies; MCP, mitoxantrone/chlorambucil/prednisone; Mel, melphalan; MINE, mesna/ifosfamide/mitoxantrone/etoposide; Mito, mitoxantrone; MTX, methotrexate; NHL, non-Hodgkin lymphoma; NT, not transformed; OS, overall survival; PBSC(T), peripheral blood stem cell (transplantation); PFS, progression-free survival; PmM, prednimustine/mitoxantrone; PR, partial remission; Ref, reference; RFS, relapse-free survival; Ritux, rituximab; RT, radiation therapy; SCT, stem cell transplantation; SLL, small lymphocytic lymphoma; T, transformed; TBI, total-body irradiation; TRM, treatment-related mortality; TT, thiotepa; Tx, treatment; VGPR, very good partial response; VP-16, etoposide; WF, Working Formulation.
*Quality and strength of evidence definitions are listed in Table 1.

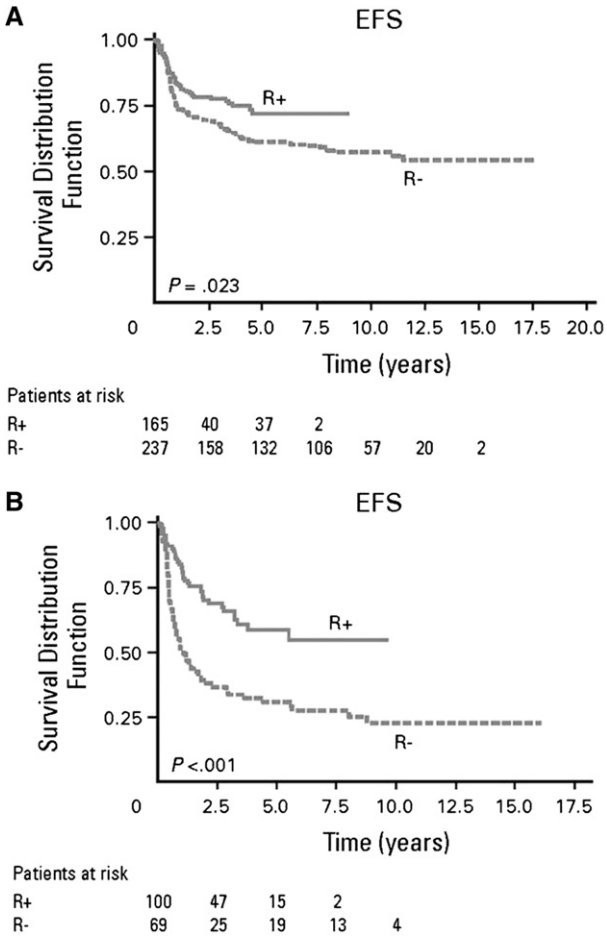

Figure 8. Estimated EFS for patients who underwent PBSCT with (R+) or without (R–) rituximab according to disease status. (A) Patients receiving PBSCT first-line therapy. (B) Patients receiving PBSCT as salvage therapy for refractory disease or early relapse. (Tarella et al., 2008 [26]. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.)

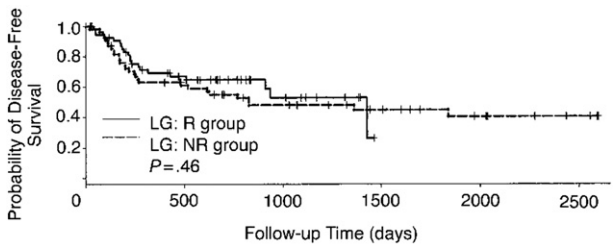

Figure 9. DFS in low-grade lymphoma patients by pre-SCT rituximab (R group) versus no rituximab (NR group). (Hoerr et al., 2004 [27]. Reprinted with permission. © 2004 American Society of Clinical Oncology. All rights reserved.)

BMT, compared to 50 matched low-grade NHL patients who underwent unpurged autologous BMT. Significantly more unpurged autologous BMT patients received a high dose therapy regimen containing TBI (28 versus 15, $P = .0164$). Although there was no significant difference in 5-year PFS between the groups, 5-year OS was significantly improved after purged autologous BMT.

Comparison of High-Dose Therapies Prior to Autologous SCT

Three studies compared two different high-dose therapy regimens prior to autologous SCT. One study reported a significantly better 5-year OS for patients receiving radioimmunotherapy versus standard high-dose therapy prior to autologous SCT. The other two studies reported no significant differences in survival outcomes comparing TBI + Cy + etoposide (VP-16) versus busulfan + melphalan + thiotepa (Bu/Mel/T), or comparing Bu + Cy versus BCNU (carmustine) + VP-16 + cytarabine + Cy (BEAC) prior to autologous SCT.

Gopal et al. [30] reported the results of a single center study of 125 adult (24-59 years) patients with relapsed FL, comparing the outcomes of 27 patients treated with high-dose anti-CD20 radioimmunotherapy (^{131}I-tositumomab) plus autologous SCT versus 98 nonrandomized control patients treated with conventional high-dose chemotherapy regimens followed by autologous SCT. Significantly more patients in the radioimmunotherapy + autologous SCT group had elevated lactate dehydrogenase (LDH) (41% versus 20%, $P = .03$) and an International Prognostic Index (IPI) score ≥2 (41% versus 16%, $P = .02$) compared to patients undergoing conventional high-dose therapy and autologous SCT. Patients receiving radioimmunotherapy prior to autologous SCT had a significantly higher 5-year OS, but not PFS, than patients receiving standard chemotherapy prior to autologous SCT.

Gutierrez-Delgado et al. [31] presented the results of a single center study of 351 adult (18-67 years) patients with NHL. Of these, 106 (30%) patients with indolent NHL underwent autologous SCT following high-dose therapy with either TBI + Cy + VP-16 (n = 76) or BuMelT, n = 30). Forty-five percent of the Bu/Mel/T patients had undergone prior radiation therapy and were not eligible to receive TBI + Cy + VP-16. Significantly more patients in the TBI + Cy + VP-16 group had BM involvement prior to HSCT (15% versus 5%, $P = .004$), whereas the Bu/Mel/T group had more patients >60 years and with aggressive histology ($P < .005$). There was no significant difference in 5-year EFS between patients in the two conditioning regimens.

Weaver et al. [32] reported the results of a multicenter study of 49 adult (25-62 years) patients with refractory or relapsed low-grade NHL (follicular lymphoma, 82%) who underwent high-dose therapy with either Bu + Cy (n = 22) or BEAC (n = 27) prior to an unpurged autologous PBSCT. BEAC patients

were significantly older ($P = .031$) and included more females ($P = .025$) than the Bu + Cy group. There was no significant difference in 3.6-year EFS or OS between patients in the two conditioning regimens.

ALLOGENEIC SCT

This section includes one comparative study described in the following section of MA versus reduced intensity conditioning (RIC) allogeneic SCT. The quality rating for this study was 2++. Table 7 provides a summary of the design, methodology, and outcomes data from this study, which found no significant difference in outcomes by conditioning regimen intensity.

Also included in this section are 12 noncomparative cohort studies of allogeneic SCT using either MA (5 studies) or RIC (7 studies) regimens. The quality ratings for these studies ranged from 2++ to 2+. The design, methodology, and outcomes data from these studies are summarized in Appendix Table 2 (online only). Overall, the outcomes data from these studies contribute to the overall understanding of the effectiveness of allogeneic SCT in the treatment of follicular lymphoma.

Myeloablative versus Reduced Intensity Allogeneic SCT

Hari et al. [33] presented the results of a multicenter, retrospective study of 208 adult (27-70 years) patients with FL reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), comparing the outcomes of those who underwent MA (n = 120) conditioning versus RIC (n = 88) prior to an HLA-identical sibling allogeneic SCT. Recipients of unrelated donor allogeneic SCT and/or *ex vivo* T cell-depleted grafts were excluded. RIC was defined by the CIBMTR as TBI <5 Gy as a single fraction, Bu doses <9 mg/kg, Mel doses ≤150 mg/m^2, and fludarabine-based regimens without MA doses of TBI, Bu, or Mel. Use of RIC increased from <10% of transplantations in 1997 to >80% of transplantations in 2002. The RIC cohort was significantly older, more likely to be in ≥CR2 at SCT, had a longer interval from diagnosis to SCT, and were more likely to have received rituximab prior to SCT, whereas the MA cohort had a higher proportion of patients with primary induction failure and a higher incidence of BM involvement. There was no significant difference in 3-year PFS or OS between patients in the MA and RIC groups.

PROGNOSTIC FACTORS

Table 8 summarizes patient- and disease-related prognostic factors found to have a positive or no impact on survival outcomes, as determined by multivariate analyses. Studies were not included in this table if they did not conduct a multivariate analysis. This table is provided for the reader's information and was not used to make treatment recommendations.

FUTURE DIRECTIONS

Areas of Needed Research

After reviewing the evidence, the expert panel identified the following important areas of needed research in FL:

1) Rituximab-based therapy followed by autologous SCT versus rituximab-based therapy without SCT.
2) Post-autologous SCT rituximab maintenance therapy versus no post-autologous SCT maintenance rituximab.
3) *Ex vivo* purged autologous SCT.
4) T cell-depleted allogeneic SCT.
5) Comparison of matched-related versus matched-unrelated or other alternative donor for allogeneic SCT.
6) The efficacy and toxicity of reduced intensity regimens before autologous and allogeneic SCT.
7) RIC allogeneic SCT as salvage therapy after failed autologous SCT.
8) Radioimmunotherapy as part of the preparatory regimen for autologous SCT or RIC allogeneic SCT.
9) The impact of radioimmunotherapy and newer agents (ie, bendamustine, rituximab, alemtuzumab, fludarabine, etc.) on stem cell quality.
10) Identification of surrogate molecular markers pre-SCT that are predictive of long-term survival in FL patients.
11) The association of FLIPI score at diagnosis and at SCT with prognosis in FL patients.

Ongoing Studies

Several studies are summarized below that address areas of needed research or other issues that may ultimately affect the treatment recommendations made in Table 3. These studies are currently accruing patients, are ongoing, or have been published in abstract form. None of the data described below was used as evidence for the review or used for making treatment recommendations. This section is provided for the reader's information only.

Rituximab Prior to Autologous SCT

Rituximab as first-line therapy

At a median follow-up of 58 months, Buske et al. [34] reported on a GLSG trial of 552 patients with newly diagnosed advanced stage follicular lymphoma

Table 7. Patient Characteristics and Outcomes from Myeloablative versus RIC Allogeneic SCT Study

Study Design			Patient Outcomes				
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocols	Diagnosis or Stage (at Dx unless stated)	Study Groups (n)	(Interval) % TRM (Significance)	(Interval) % Relapse (Significance)	(Interval) % DFS/RFS/PFS/EFS (Significance)	(Interval) % OS (Significance)
[33]	*Pre-SCT Ritux:*	FL 100%	(HLA-identical Sib Donors)	(3-year TRM)	(3-yr Relapse)	(3-year PFS)	(3-year OS)
Hari et al. 2008	MAT 26%						
2++	RIC 45%	Mostly Ref/Rel	MAT Allo SCT (120)	25%	8%	67%	71%
1997-2002			[4.2 y (0.3-8 y)]	CI 17-33%	CI 4-14%	CI 58-75%	CI 63-79%
CIBMTR	*Prior Auto SCT:*	Status at SCT					
Multicenter (> 500)	MAT 6%	MAT	RIC Allo SCT (88)	28%	17%	55%	62%
n=208	RIC 10%	Refractory 36%	[2.9 y (0.3 -6.8 y)]	CI 19-38%	CI 10-26%	CI 44-65%	CI 51-72%
		CR1 8%					
Med Age (range):	*Conditioning:*	≥ CR2 11%		(*P* = .60)	(*P* = .06)	(*P* = .07)	(*P* =.15)
MAT 44 y (27-70 y)	MAT Cy + TBI 67%	≥1 Relapse 45%					
RIC 51 y (27-70 y)	Bu + Cy 25%						
	TBI only 8%	RIC					
Med Chemo Reg (range):		Refractory 26%					
Not stated (1- ≥ 4)	RIC Flu + Cy 42%	CR1 3%					
	Flu + Bu 25%	≥ CR2 22%					
Med Dx to SCT (range):	Flu + Mel ± ATG 18%	≥1 Relapse 49%					
MAT 2.1 y (0.3-16.5 y)	Flu + TBI 10%						
RIC 3 y (0.5-16.3 y)	Other 5%						

Allo indicates Allogeneic; ATG, Antithymocyte globulin; Bu, Busulfan; Chemo, Chemotherapy; CI, 95% Confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, Complete remission; Cy, Cyclophosphamide; DFS, Disease-free survival; Dx, Diagnosis; EFS, Event-free survival; FL, Follicular lymphoma; Flu, Fludarabine; HLA, Human leukocyte antigen; MAT, Myeloablative therapy; Mel, Melphalan; OS, Overall survival; PFS, Progression-free survival; RFS, Relapse-free survival; Ref, Reference; RIC, Reduced intensity conditioning; SCT, Stem cell transplantation; Sib, sibling; TBI, Total body irradiation; TRM, Treatment-related mortality

*Quality and strength of evidence definitions are listed in Table 1.

randomized between R-CHOP versus CHOP, followed by a second randomization in responding patients <60 years to IFN-α maintenance versus MA chemotherapy plus autologous SCT. All patients ≥60 years received IFN-α maintenance. Five-year OS was significantly improved for R-CHOP versus CHOP (90% versus 84%, $P = .049$), but only in patients who did not undergo autologous SCT (OS; IFN-α, 78% versus auto SCT, 66%, $P = .43$).

Rituximab as salvage therapy

Weigert et al. [35] reported the outcome of autologous SCT after the addition or not of rituximab to salvage regimens in 167 adult (19-64 years) patients with relapsed or refractory follicular lymphoma in a retrospective analysis of 2 randomized, multicenter GLSG trials (MCP versus CHOP and CHOP versus R-CHOP, both followed by randomization to IFN-α maintenance versus autologous SCT). The median PFS and OS for patients treated with or without rituximab were 3.4 versus 2.8 years and 8.3 versus 7.2 years, respectively. Sixty-six patients (40% of eligible) received autologous SCT, 31 of whom were treated with prior rituximab. The median PFS for patients receiving autologous SCT or not was 5.5 versus 2.3 years ($P = .038$), respectively. Subgroup analysis found that the addition of rituximab to salvage therapy primarily benefited patients who did not undergo autologous SCT.

Rituximab as *in vivo* purging pre-SCT and maintenance therapy post-SCT

The EBMT Solid Tumors Working Party has sponsored a Phase III, randomized, multicenter trial (NCT00005589) comparing combination chemotherapy and autologous PBSCT with or without rituximab as *in vivo* purging pre-SCT and maintenance therapy post-PBSCT in adult (≥18 years) patients with relapsed FL. A total accrual of 460 patients (115 to each of 4 treatment arms) is projected. Time to disease progression is the primary outcome measure, with response rate, survival, and molecular remission rates as secondary outcome measures of interest.

Rupolo et al. [36] reported the outcomes of 34 adult (30-66 years) patients enrolled between 2002 and 2007 in a nonrandomized, single-center study. Patients who responded to salvage therapy (R-DHAOX) underwent high-dose chemotherapy with BEAM-R, followed by autologous SCT, followed by maintenance therapy with rituximab for two years. Sixty-eight percent of patients had FL, 29% had mantle cell, and one patient had transformed FL. At 32 months follow-up from salvage therapy, 5-year projected PFS was 78% for FL patients.

Cheung et al. [37] reported the outcomes of 29 adult (30-65 years) patients with relapsed high-risk FL enrolled in a single center Phase II study investigating the impact of achieving a molecular remission after *in vivo* purging with rituximab and post-SCT

Table 8. Patient and Disease-Based Prognostic Factors Found to Have a Positive Impact on Survival* Outcomes as Determined by Multivariate Analysis in the Referenced Studies

Favorable Prognostic Factor†	Studies Reporting Significant Positive Impact of Prognostic Factor on Survival	Studies Reporting No Impact of the Prognostic Factor on Survival
PATIENT-RELATED FACTORS		
Younger age	20, 27, 45, 55, 59, 61, 63, 69, 70, 73, 74, 83, 84, 85	44, 46, 47, 56, 64, 68, 71, 72
Female gender	46	25, 44, 47, 55, 64
DISEASE-RELATED FACTORS		
Early stage (versus advanced or transformed)	20, 31, 60, 61, 62, 68	24, 44, 45, 47, 72
Less aggressive histology (FL versus DLBCL)	26, 31, 48, 82, 83, 84	55, 64, 65, 71
Better performance status (ECOG ≤2 or Karnofsky ≥90)	9, 13, 20, 33, 74, 82	12
No prior bone marrow involvement	23, 47, 58, 64	46, 56, 73
Lower serum LDH at diagnosis	20	12, 44, 46, 72
Lower serum LDH at SCT	30, 45, 61	55
Fewer extranodal sites	12, 13, 45, 46	44, 47, 70, 72
Lower FLIPI or IPI score (≤2)	26, 30, 60, 63	13, 44, 47, 50
No B symptoms	9, 76	
No bulky disease at diagnosis	47	55, 70, 72
No bulky disease at SCT		68, 73
TRANSPLANTATION-RELATED FACTORS		
Chemosensitivity (in CR at SCT)	9, 20, 23, 26, 33, 45, 55, 59, 61, 68, 69, 73, 74, 78, 80, 83	24, 46, 49, 63, 64, 65, 70, 71, 72, 82
Fewer courses or lines of chemotherapy	24, 27, 55, 57, 58, 61	23, 45, 46, 49, 52, 56, 59, 62, 73
Molecular remission after SCT	9, 44, 48, 51, 54, 57, 63	55, 68
Use of autologous SCT (versus other therapy)	9, 12, 13, 20, 23	
Non-TBI or f-TBI-based therapy	29, 57, 61, 74	55, 68
Shorter interval from diagnosis to SCT	20, 48, 82	24, 45, 59, 63, 68, 72
Use of rituximab pre-SCT or salvage	26, 72	28, 45, 64
Purged autologous BMT (versus unpurged)	21, 29	25, 63
No development of acute GVHD grades 3-4	76, 78	
Transplantation after mid-1990s	20	73
Auto SCT as first-line therapy (versus as salvage therapy)	25	52
Methotrexate-containing GVHD prophylaxis	82	
Large transplantation center	29	

BMT indicates bone marrow transplantation; CR, complete remission; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; f-TBI, fractionated total-body irradiation; GVHD, graft-versus-host disease; IPI, International Prognostic Index; LDH, lactate dehydrogenase; SCT, stem cell transplantation; TBI, total-body irradiation.
Quality and strength of evidence definitions are listed in Table 1.
*Survival = any 1 or more of the following: OS, DFS, EFS, FFS, LFS, PFS, RFS.
†Factors were not included if the study did not conduct a multivariate analysis.

maintenance immunotherapy with rituximab plus IFN-α. Of the 17 grafts purged with rituximab, 8 still had molecular disease pre-SCT. Of 16 assessable patients post-SCT, 11 achieved molecular remission prior to maintenance immunotherapy, and all 16 achieved molecular remission during maintenance. Median PFS for all patients is 50 months; median OS has not been reached.

Chemotherapy + IFN-α versus autologous PBSCT + IFN-α maintenance

The European Organization for Research and Treatment of Cancer (EORTC) has sponsored a randomized, multicenter, Phase III trial (NCT 00003152) to compare the effectiveness of combination chemotherapy followed by IFN alone versus combination chemotherapy plus radiation and autologous PBSCT ± IFN-α maintenance for treating adult (18-65 years) patients with *de novo* stage III or IV FL. A total accrual of 469 patients is projected. PFS, OS, and toxicity are the primary outcome measures.

Radioimmunotherapy and Autologous SCT

Gisselbrecht et al. [38] reported the outcomes of 77 adult (31-64 years) patients with relapsed or refractory low grade lymphoma (90% FL) enrolled in a Phase II GELA study investigating the efficacy of 90ttrium ibritumomab tiuxetan (Zevalin) + BEAM (Z-BEAM) followed by autologous SCT as a salvage regimen. Most patients (96%) had received rituximab as part of their salvage regimen. After a minimum follow-up of 1 year for all patients, the estimated 2-year EFS is 93%. No toxic deaths were observed.

Reduced-intensity conditioning (RIC) regimens

Autologous SCT versus RIC allogeneic SCT

Robinson et al. [39] compared the outcomes of 1504 adult (20-73 years) patients who underwent

either an autologous (n = 1394) or RIC HLA-matched sibling or HLA-matched unrelated donor allogeneic (n = 110) SCT between 1998 and 2005 and were reported to the EBMTR. At a median follow-up of 26 months post-SCT, the 3-year PFS was 62% versus 58% (*P* not stated) for patients who underwent RIC allogeneic SCT versus autologous SCT, respectively.

Laport et al. [40] reported the outcomes of 30 adult (36-66 years) patients with relapsed FL enrolled in the CTN0202 multicenter trial, comparing the efficacy and toxicity of autologous SCT (n = 22) versus RIC allogeneic SCT (n = 8). Patients were assigned to treatment based on the availability of an HLA-matched related donor. This trial closed early because of slow accrual. At a median follow-up of 16 months, RIC allogeneic SCT patients had superior 2-year PFS compared to the autologous SCT patients (100% versus 69%, respectively, $P = .04$). OS was 100% versus 80% (*P* not stated) for RIC allogeneic versus autologous SCT, and nonrelapse mortality was 0% and 15%, respectively (*P* not stated).

MA versus RIC allogeneic SCT

Sureda et al. [41] compared the outcomes of 144 patients with FL treated between 1991 and 2005 with RIC (n = 93) versus myeloablative conditioning (n = 41) followed by an HLA-matched unrelated donor allogeneic SCT and reported to the EBMT registry. Forty-seven percent of patients had previously undergone a failed autologous SCT. RIC patients had significantly longer 3-year PFS (43% versus 35%, $P = .004$) and OS (49% versus 40%, $P = .001$) than those treated with MA conditioning prior to allogeneic SCT. The 3-year nonrelapse mortality was 34% and 46% ($P < .001$) for the RIC and MA conditioning groups, respectively.

RIC allogeneic SCT

Corradini et al. [42] reported the outcomes of 194 patients with relapsed or refractory lymphomas (35% low-grade NHL) enrolled in a prospective, multicenter, Phase II study of the long-term outcomes of RIC consisting of Cy + thiotepa + fludarabine followed by allogeneic SCT from sibling donors. Median follow-up was 5 years. The 5-year OS and PFS were 62% and 70% for low-grade NHL.

Khouri et al. [43] reported the long-term outcomes of 47 adult (33-68 years) patients with recurrent chemosensitive FL enrolled in a prospective, single-center, Phase II study of RIC with Flu + Cy + rituximab followed by an HLA-matched related (n = 45) or unrelated (n = 2) donor allogeneic SCT. At a median follow-up of 56 months, the 6-years OS and PFS rates were 85% (95% confidence interval [CI], 71%-93%) and 83% (95% CI, 69%-91%), respectively.

STRENGTHS/LIMITATIONS AND DISCUSSION

The strengths of this systematic evidence-based review are the details conveyed in the text about each study's design, the presentation of outcomes in summary tables for each major section, and the treatment recommendations made by the FL expert panel. A limitation is the exclusion of nonpeer-reviewed data. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. Data published in abstract form were not included because of the inadequate details of study design or patient characteristics, making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial difficult.

A limitation of the FL literature is that there is no consistency in the survival estimate time points, making it difficult to compare outcomes across studies. FL is an indolent disease requiring long follow-up intervals; however, longer follow-up leads to delayed publication, making it problematic to reflect up-to-date information. Although many studies in this review reported short (<5 years) follow-up intervals, much of the evidence presented in this review does not reflect current clinical practice. For example, most of the reviewed studies were conducted prior to the U.S. FDA approval of rituximab; therefore, the assumption of a benefit of rituximab pre-SCT for FL has been extrapolated from evidence of its use in aggressive NHL. The lengthy process of conducting and reporting clinical research emphasizes the need to identify surrogate molecular markers that are predictive of long-term survival in FL patients. In addition, further delineation of clinical risk factors may facilitate appropriate selection of follicular lymphoma patients for autologous versus allogeneic SCT.

A related limitation is that a number of FL studies revealed plateaus on the Kaplan-Meier survival curves, but did not always report how patients were followed-up (passively or actively) or for how long. Retrospective analyses of registry data are good for obtaining long-term follow-up, but patients are heterogeneously treated, whereas randomized controlled trials homogeneously treat patients, but usually present data with shorter follow-up. This differential follow-up could lead to under-reporting of MDS/AML incidence, relapse rate, and late mortality.

REFERENCES CITED IN ONLINE APPENDIX TABLES

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbmt.2010.01.008.

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