REVIEW

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Diffuse Large B Cell Lymphoma: Update of the 2001 Evidence-Based Review

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Clinical research published since the 2001 evidence-based review on the role of hematopoietic stem cell transplantation (SCT) in the treatment of diffuse large B cell lymphoma (DLBCL) in adults is presented and critically evaluated in this update. Treatment recommendations that remain unchanged from the original review include: (1) autologous SCT as salvage therapy is recommended for patients with chemosensitive relapsed DLBCL; and (2) autologous SCT is not recommended for patients who achieve a partial response to an abbreviated induction regimen. New treatment recommendations based on new published data include: (1) autologous SCT as first-line therapy is not recommended for any IPI group; (2) planned tandem or multiple sequential autologous SCT is not recommended; (3) peripheral blood is the standard stem cell source for autologous SCT; (4) age is not a contraindication for autologous SCT, although outcomes in older adults are not as good as in younger adults. There are insufficient data to make recommendations on the routine use of rituximab maintenance after autologous SCT, autologous versus allogeneic SCT, fewer versus more cycles of induction therapy prior to autologous SCT, or the use of reduced intensity versus myeloablative conditioning regimens. Areas of needed research in the treatment of DLBCL with SCT were identified and are presented in the review.

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INTRODUCTION

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began the development of systematic evidence-based reviews (EBR) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately 5-year intervals. This constitutes the first EBR in the series to be updated.

UPDATE OF THE 2001 DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) EVIDENCE-BASED REVIEW

It is important to note that the study inclusion criteria, the systems for grading the quality and strength of the evidence and the strength of the treatment recommendations, and the format of the reviews have changed considerably since the original DLBCL EBR was published. The DLBCL update adheres to the methodology and grading systems presented in Appendix A (online only). In the original DLBCL EBR [1], each article was summarized in detail in the

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Table 1. Summary of Updated Treatment Recommendations for Diffuse Large B Cell Lymphoma

Indication for SCT	Original versus New Rec	Tx Rec Grade*	Highest Level of Evidence†	Ref. No.‡	Treatment Recommendation Comments
Autologous SCT versus nontransplantation as first-line therapy	New recommendation based on new data published since the original review	A	1++	[2-7, 9-11] (Table 2)	Autologous SCT as first-line therapy is not recommended for any IPI group at this time. None of the published studies included rituximab in their protocols. Ongoing studies, which include rituximab, may change this recommendation.
Autologous SCT versus nontransplantation as therapy for patients who achieve a partial response to 3 cycles of induction	Original recommendation is unchanged with no new data published since the original review	A	1+	[18] (Table 3)	Autologous SCT is not recommended for patients who achieve a partial response to an abbreviated (3 cycles) induction regimen.
Autologous SCT versus nontransplantation as salvage therapy	Original recommendation is unchanged with no new data published since the original review	A	1+	[19] (Table 4)	Autologous SCT provides a significant survival benefit and is recommended as part of salvage therapy for patients with chemosensitive relapsed DLBCL.
TRANSPLANTATION TECHNIQUES					
Autologous SCT as salvage therapy for patients aged >60 years	New recommendation based on new data published since the original review	B	2+	[20-22] (Table 5)	Older age (>60 years), in and of itself, is not a contraindication for autologous SCT as long as other SCT eligibility criteria are met. No upper age limit has been defined. However, outcomes (TRM, relapse, survival) in older adults are not as good as in younger adults.
Autologous versus ablative allogeneic SCT	No treatment recommendation based on new data published since the original review		2++	[23] (Table 6)	Overall survival outcomes are equivalent for autologous and allogeneic SCT; neither option is recommended over the other. Autologous and allogeneic SCT have competing risks with regard to relapse and TRM. Comparison of these two techniques is biased by different patient selection criteria.
Bone marrow versus peripheral blood as the stem cell source for autologous SCT	New recommendation based on new data published since the original review	A	1++	[25] (Table 7)	Autologous PBSCT provides no survival benefit or improved tumor control compared to autologous BMT. However, PBSCT is safer and easier to use with faster engraftment and lower rate of deaths because of infection, hence peripheral blood is the standard for stem cell source. Of note, 98% of recent autologous SCTs use peripheral blood as the stem cell source.§
Rituximab as maintenance therapy after autologous SCT	No treatment recommendation based on new data published since the original review		1+	[26] (Table 7)	There are insufficient data to recommend routine post-autologous SCT maintenance with rituximab outside of a clinical trial. One randomized study with short follow-up reported a nonsignificant difference in EFS with rituximab as maintenance after autologous SCT.
Fewer versus more cycles of induction therapy prior to first-line autologous SCT	No treatment recommendation based on new data published since the original review		2++	[27] (Table 7)	Based on one study, there are insufficient data to make a treatment recommendation regarding fewer versus more cycles of induction therapy prior to first-line autologous SCT.
Multiple or tandem autologous SCT	New recommendation based on new data published since the original review	B	2+	[44-47] (Appendix C)	Based on evidence from phase II trials, planned tandem or multiple

(*Continued*)

Table 1. (*Continued*)

Indication for SCT	Original versus New Rec	Tx Rec Grade*	Highest Level of Evidence†	Ref. No.‡	Treatment Recommendation Comments
					sequential autologous SCTs are not recommended.
Reduced intensity versus myeloablative conditioning for allogeneic SCT	No treatment recommendation based on new data published since the original review		2+	[28] (Table 8)	Based on one study and expert opinion, RIC appears to be an acceptable alternative approach for selected patients who cannot tolerate a myeloablative regimen. However, longer follow-up is needed to clarify the competing risks of relapse and chronic GVHD and their impact on overall survival and quality of life. Comparison of these regimen intensities are biased by patient selection criteria which have changed over time.

BMT indicates bone marrow transplantation; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; GVHD, graft-versus-host disease; IPI, International Prognostic Index; PBSCT, peripheral blood stem cell transplantation; SCT, stem cell transplantation; TRM, treatment-related mortality.

*__Definitions:__ **Grade of Recommendation** (Appendix A, Table 2, online only): (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+.

†__Definitions:__ **Levels of Evidence** (Appendix A, Table 1, online only): 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-control 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 each section of the review.

§Based on CIBMTR data from 2002-2006.

text, accompanied by summary tables comparing patient outcomes. To streamline this update, a concise summary of each section will be provided in the text, whereas descriptions of the study design, patient population, and clinical outcomes of each article will be presented in detailed summary tables.

TREATMENT RECOMMENDATIONS

In this DLBCL update, Table 1 contains the summary of consensus treatment recommendations made by the expert panel based on the summarized evidence. The consensus process is detailed in Appendix A (online only) and 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 Appendix A, Table 2.

Table 1 presents new treatment recommendations based on the DLBCL evidence published since 2000. In addition, the recommendations from the original EBR are incorporated into the table when applicable, regraded according to the schema in Appendix A, Table 2, and notated as to whether new evidence strengthens, weakens, or does not change the original recommendation.

AUTOLOGOUS SCT VERSUS NONTRANSPLANTATION THERAPY

Autologous SCT versus Nontransplantation as First-line Therapy

Published since the original EBR are two meta-analyses and nine prospective, multicenter, randomized studies comparing the efficacy of full-course chemotherapy versus abbreviated (typically <4 cycles) and/or high-dose sequential chemotherapy regimens followed by autologous SCT as first-line treatment for patients with *de novo* DLBCL. Table 2 presents a detailed summary of the study designs, patient populations, and outcomes from this new evidence. Rituximab was not part of the protocol in any of these studies. Three Phase III studies from the original DLBCL EBR that compared autologous SCT versus nontransplantation therapy, and that met current inclusion criteria (full-length, peer-reviewed articles), are also presented in Table 2 according to the new format and grading criteria.

Table 2. Autologous SCT versus Nontransplantation as First-Line Therapy for DLBCL

Study Design							Patient Outcomes			
	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)					Treatment Group		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) and Pt. Outcomes	Control (n)	Transplant (n)	*P*
UPDATE DATA (POST-2000 STUDIES)										
META-ANALYSES OF AUTOLOGOUS SCT VERSUS CHEMO AS FIRST-LINE THERAPY										
[2] Greb 2007	**Chemo**	**Auto SCT**		**Chemo**	**Auto SCT**			**Chemo**	**Auto SCT**	
1++	Full or sequential therapy with variety of combination chemo regimens	Full induction, Abbreviated, or Sequential high-dose therapies	*Diagnoses de novo* aggressive NHL	100%	100%		Relative risk to achieve CR	RR 1.11 favoring Auto SCT (CI 1.04-1.18)		
Meta-analysis Search from 1990-1/2005 15 Randomized trials 11 Full-text; 4 Abstracts Summary data Total n = 2728		BM, PBSC, or both for Auto SCT					TRM (14 studies, N = 2555)	4.3% (55/1274)	5.7% (73/1281)	>.05
							HR for EFS (12 studies, n = 1795)	HR 0.92 (CI 0.80-1.05) No significant difference in EFS between Tx groups		
							HR for OS (14 studies, n = 2444)	HR 1.05 (CI 0.92-1.19) No significant difference in OS between Tx groups		
							OS Subgroup Analysis by aaIPI (12 studies)			
							Good risk	HR 1.46 (CI 1.02-2.09) Impaired OS for SCT pts, *P* = **.032**		
							Poor risk	HR 0.95 (CI 0.81-1.11) No difference in OS by Tx		
[3] Strehl 2003	**Chemo**	**Auto SCT**		**Chemo**	**Auto SCT**			**Chemo**	**Auto SCT**	
							Mortality	36.4% (406/1115)	36.9% (411/1113)	.80
1++	Full or sequential therapy with variety of combination chemo regimens	Full induction, Abbreviated, or Sequential high-dose therapies BM, PBSC, or both for Auto SCT	*Diagnoses de novo* intermediate or high risk aggressive NHL	100%	100%		Heterogeneity among studies	$\chi^2 = 33$		**.0003**

(*Continued*)

Table 2. (*Continued*)

Study Design							Patient Outcomes			
	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)					Treatment Group		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) and Pt. Outcomes	Control (n)	Transplant (n)	*P*
Meta-analysis Search thru March, 2003 11 Randomized trials 9 Full-text; 2 Abstracts Summary data Total n = 2228							*Mortality based on Induction Intensity:* Full course (2 studies, n = 655)	33.2% (111/334)	31.7% (105/331)	.70
							Shortened (n = 1341)	35.7% (238/667)	39.9% 269/674)	.12
							HDS (2 studies, n = 228)	47.4% (54/114)	30.1% (33/108)	**.01**
							Mortality based on IPI (7 studies, n = 1280):			
							I-H + H Risk	45.6% (273/651)	41.3% (287/629)	.40
							I-H + H Risk + Full course Induction (2 studies, n = 306)	49.7% (73/147)	35.2% (56/159)	**.01**
							I-H + H Risk + Shortened Induction (4 studies, n = 850)	44.3% (185/418)	44.7% (193/432)	.80
STANDARD CHEMO VERSUS ABBREVIATED CHEMO + AUTOLOGOUS SCT										
[4] Gisselbrecht 2002 1++ 1993-1995 GELA LNH93-3 Multictr (18) Prospective Randomized n = 370 *Med Age (range)* 46 y (15-60)	**ACVBP** 4× ACVBP + GF 2× MTX 4× VP-16 + Ifo 2× Ara-C	**HDT + Auto PBSCT** 1× CEOP + MTX 2× ECVBP + GF BEAM Auto PBSC	*Diagnoses* *de novo* aggressive NHL *Hist. Subtypes* DLBCL Nonanaplastic T cell Anaplastic T cell Lymphoblastic Burkitt	**ACVBP** 100% 62.5% 10.5% 10.5% 4% 0.5%	**HDT + Auto PBSCT** 100% 60% 19% 5% 3% 3%	.07	(5 y, not stated) (ITT) Completed Assigned Tx Overall CR TRM 5-year EFS	**ACVBP** (181) Not stated 64% Not stated 51 ± 8	**HDT + Auto PBSCT** (189) 74% 63% 1% 39 ± 8	**.01**

(*Continued*)

Table 2. (*Continued*)

Study Design							Patient Outcomes			
	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)					Treatment Group		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) and Pt. Outcomes	Control (n)	Transplant (n)	*P*
			Diffuse, aggress, unclassifiable	12%	10%		5-year OS	60 ± 8	46 ± 8	**.007**
			B symptoms	67%	73%	.20	*For aaIPI ≥3*			
							5-year EFS	47%	40%	.50
			BM Involvement	26%	32%	.20	5-year OS	52%	48%	.90
			Bulky Disease	48%	44%	.40				
			Risk Factors							
			age >40 y	62%	67%	.30				
			aaIPI ≥3	35.5%	34%	.40				
			Stage ≥III	95%	94%	.50				
			LDH ≥Normal	91%	94%	.17				
			>1 Ex-nodal sites	54%	72%	**.0004**				
			PS ≥1	47%	45%	.40				
[5] Kaiser 2002	**CHOEP**	**CHOEP + Auto SCT**		**CHOEP**	**CHOEP + Auto SCT**	Not stated	(3.8 y, Not stated)	**CHOEP**	**CHOEP + Auto SCT**	
1++	5× CHOEP	3× CHOEP + GF	*Diagnoses de novo* aggressive NHL	100%	100%		(ITT)	(154)	(158)	
1990-1997	(± RT for bulky dis.)						Completed Assigned Tx	89%	65%	
German HG NHL Multictr (71)		BEAM	*Hist. Subtypes* DLBCL	61%	58%					
Prospective		Auto PBSC or BM	PMBL	16%	9%		Overall CR	62.9%	69.9%	
Randomized n = 312			Anaplastic LCL	10%	9%					
		(± RT for bulky dis.)	Lymphoblastic or Burkitt	5%	11%		TRM		2.6% total†	
Med Age (range) 46 y (19-60)			Peripheral T cell	4%	3%		3-year EFS	49%	59%	.22
			Other	4%	10%					
							3-year OS	63%	62%	.68
			Bulky Disease	58%	61%					
							Secondary Disease	2.5%	1%	
			Risk Factors							
			age >50 y	37%	35%					
			IPI ≥3	75%	73%					
			Stage ≥III	63%	66%					
			LDH >400 U/L	50%	50%					
			PS > 2	13%	16%					
[6] Kluin-Nelemans 2001	**Chemo**	**HDT + Auto BMT**		**Chemo**	**HDT + Auto BMT**	Not stated	(4.4 y, 3.9-4.8 y)	**Chemo**	**HDT + Auto BMT**	
1++	8× CHVmP/BV	6× CHVmP/BV + GF	*Diagnoses de novo* aggressive NHL	100%	100%		(ITT)	(96)	(98)	

(*Continued*)

Table 2. (*Continued*)

Study Design							Patient Outcomes			
	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)					Treatment Group		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) and Pt. Outcomes	Control (n)	Transplant (n)	*P*
1990-1998	(± RT for bulky dis.)						Completed			
EORTC Multictr (300+)		BEAC	*Hist. Subtypes*				Assigned Tx	85%	61%	
Prospective			DLBCL	58%	50%					
Registered n = 311		Auto BM	Anaplastic	12%	18%		Overall CR	58%	69%	
Randomized n = 194			PMBL	2%	2%					
		(± RT for bulky dis.)	Marginal B cell	3%	2%		NRM	15%	15%	
Med Age (range)			Mantle cell	3%	1%					
Chemo 44 y (16-63)			Peripheral T cell	2%	1%		5-year PFS	56%	61%	>.05
HDT + Auto 41 y (16-65)			Other	3%	2%			CI 45%-67%	CI 51%-72%	
			Unclassifiable	12%	20%					
			Ineligible (included)	5%	4%		5-year OS	77%	68%	>.05
								CI 67%-86%	CI 57%-79%	
			B symptoms	37%	36%					
			BM Involvement	11%	15%					
			Bulky Disease	42%	46%					
			Risk Factors							
			age >60 y	2%	3%					
			aaIPI ≥3	29%	31%					
			Stage ≥III	52%	57%					
			LDH >Normal	50%	47%					
			>2 Ex-nodal sites	9%	10%					
[7] Martelli 2003	**MACOP-B**	**MACOP-B + Auto PBSCT**		**MACOP-B**	**MACOP-B + Auto PBSCT**		(2 years, Not stated)	**MACOP-B**	**MACOP-B + Auto PBSCT**	
1++			*Diagnoses*					(75)	(75)	
	12× MACOP-B	8× MACOP-B	*de novo*				(ITT)			
			IG or HG NHL	100%	100%					
1994-1999	(± RT for bulky dis.)	BEAC					Completed			
Multictr (18)			*Hist. Subtypes*				Assigned Tx	84%	60%	
Prospective		Auto PBSC	DLBCL	81%	70%					
Randomized n = 150		+ GF	Peripheral T-cell	12%	7%		Overall CR	68%	76%	>.10
			Anaplastic	4%	15%	**<.05**				
Med Age (range)		(± RT for bulky dis.)	LC, unspecified	3%	8%		TRM	1%	3%	
MACOP-B 45 y (18-60)										
MACOP-B + Auto			*B symptoms*	46%	58%		5-year PFS	49%	61%	.21
41 y (19-60)								CI 29%-43%	CI 36%-49%	
			BM Involvement	17%	16%					
							5-year OS	65%	64%	.95
			Bulky Disease	45%	53%			CI 40%-53%	CI 40%-53%	
			Risk Factors				Secondary			
			IPI ≥3	35%	32%		Neoplasias	0%	0%	
			Stage ≥III	95%	86%					
			LDH > Normal	91%	85%					
			PS ≥2	51%	61%					

(*Continued*)

Table 2. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Study Design: Protocols by Treatment Group — Control Therapy	Transplant Therapy	Disease Characteristics (at Dx Unless Stated) — Disease Characteristic	Control Group	Transplant Group	*P*	Patient Outcomes — Follow-up (Med, Range) and Pt. Outcomes	Treatment Group — Control (n)	Transplant (n)	*P*
[8] Milpied 2004	**CHOP**	**HDT + Auto PBSCT**		**CHOP**	**HDT + Auto PBSCT**		(4 years, Not stated)	**CHOP**	**HDT + Auto PBSCT**	
1+			*Diagnoses*					(99)	(98)	
	8× CHOP	2× CEEP + GF	*de novo*				(ITT)			
			IG or HG NHL	100%	100%					
1994-1999	(± RT for bulky dis.)	Ara-C + MTX					Completed			
GOELAMS Multictr (16)		BEAM + GF	*Hist. Subtypes*			.30	Assigned Tx	72%	85%	
Prospective			DLBCL	75%	78%					
Randomized n = 197		Auto PBSC	Anaplastic	5%	10%		Overall CR	62%	81%	
			Diffuse, unspec.	4%	7%					
Med Age (range)		(± RT for bulky dis.)	T cell lymphoma	16%	5%		TRM	1%	3%	
CHOP 50 y (20-60)										
HDT + Auto 45 y (15-60)			*BM Involvement*	24%	33%	.20	5-year EFS	37 ± 5%	55 ± 5%	**.037**
			Risk Factors				5-year OS	56 ± 5%	71 ± 5%	.076
			Age >50 y	44%	32%	.07				
			aaIPI ≥3	49%	57%	.50	*For aaIPI < 3*			
			Stage ≥III	78%	84%	.50	5-year EFS	45%	54%	.90
			LDH >Normal	52%	56%	.12	5-year OS	68%	66%	.40
			>1 Ex-nodal sites	19%	29%					
			PS ≥2	19%	10%	.11	*For aaIPI ≥ 3*			
							5-year EFS	28 ± 6%	56 ± 7%	**.003**
							5-year OS	44 ± 7%	74 ± 6%	**.001**
STANDARD CHEMO VERSUS HIGH DOSE SEQUENTIAL (HDS) THERAPY (± ABBREVIATED CHEMO) + AUTO SCT										
[9] Olivieri 2005	**VACOP-B**	**HDS + Auto PBSCT**		**VACOP-B**	**HDS + Auto PBSCT**	Not stated	(4.4 y, 0.2-8.2 y)	**VACOP-B**	**HDS + Auto PBSCT**	
1++			*Diagnoses*					(106)	(117)	
	12× VACOP-B	8× VACOP-B	*de novo*				(ITT)			
		↓	aggressive NHL	100%	100%					
1995-2001	(± RT for bulky dis.)	Cy + GF					Completed			
NHLCSG Multictr (18)		↓	*Hist. Subtypes*				Assigned Tx	100%	68%	
Prospective		VP-16	DLBCL	83%	74%					
Randomized n = 223	If PR/NR after	↓	Anaplastic LC	12%	15%		Overall CR	76%	73%	.06
	12× VACOP-B	BEAM	Other, Inelig.	0%	4%					
Med Age (range)	↓	↓	Unclassifiable	4%	7%		TRM	1%	4%	
VACOP-B 42 y (15-60)	Cy + VP-16	Auto PBSC	Missing	1%	0%					
HDS + Auto 46 y (18-59)	+ GF, BEAM +						7-year PFS	44.9± 5.1%	40.9 ± 7.7%	.70
	Auto PBSCT ± RT	(± RT for bulky dis.)	*B symptoms*	48%	46%					
							7-year OS	60 ± 5.4%	57.8 ± 5.2%	.50
	If Relapse		*BM Involvement*	19%	25%					
	after CR to						Secondary			
	12× VACOP-B		*Bulky Disease*	37%	39%		Neoplasias	2%	2%	

(*Continued*)

Table 2. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Study Design: Protocols by Treatment Group — Control Therapy	Study Design: Protocols by Treatment Group — Transplant Therapy	Disease Characteristics (at Dx Unless Stated) — Disease Characteristic	Control Group	Transplant Group	P	Patient Outcomes — Follow-up (Med, Range) and Pt. Outcomes	Treatment Group — Control (n)	Treatment Group — Transplant (n)	P
	↓									
	2× DHAP, BEAM +		*Risk Factors*				*For aaIPI* ≥3			
	Auto PBSCT ± RT		aaIPI ≥3	68%	72%		7-year PFS	35.8%	40.7%	.50
			Stage ≥III	81%	84%		7-year OS	49.6%	47.8%	.60
			LDH >Normal	64%	54%					
			>2 Ex-nodal sites	22%	23%					
			PS ≥2	14%	22%					
[10] Betticher 2006	**CHOP**	**HDS + Auto PBSCT**		**CHOP**	**HDS + Auto PBSCT**	All >.05	(4 y, Not stated)	**CHOP**	**HDS + Auto PBSCT**	
1++			*Diagnoses*					(59)	(70)	
	6-8× CHOP	APO or CHOP	*de novo*				(ITT)			
		↓	aggressive NHL	100%	100%					
1997-2003‡	(± RT for bulky dis.)	Cy + GF					Completed			
MISTRAL Multictr (6)		↓	*Hist. Subtypes*				Assigned Tx	84%	63%	
Prospective		VCR + MTX	DLBCL	69%	76%					
Randomized n = 129		↓	PMBL	15%	17%		Overall CR	68%	66%	
		VP-16 + GF	Anaplastic	15%	7%					
Med Age (range)		↓	Unknown	1%	0%		TRM	3%	4%	
CHOP 46 y (18-61)		Mito + Mel + GF								
HDS + Auto 49 y (18-61)		↓	*B symptoms*	59%	44%		3-year EFS	33%	39%	.67
		Auto PBSC								
			BM Involvement	22%	23%		3-year OS	53%	46%	.48
		(± RT for bulky dis.)						CI 39%-67%	CI 34%-58%	
			Bulky Disease	76%	67%					
			Risk Factors							
			IPI ≥3	88%	82%					
			Stage ≥III	76%	70%					
			LDH >Normal	90%	87%					
			Ex-nodal involvement	27%	21%					
			PS ≥2	45%	27%					
[11] Vitolo 2005	**MegaCEOP**	**HDS + Auto PBSCT**		**Mega CEOP**	**HDS + Auto PBSCT**		(6.5 y, Not stated)	**MegaCEOP**	**HDS + Auto PBSCT**	
			Diagnoses					(66)	(60)	
1++	6-8× MegaCEOP	1-2× APO	*de novo* DLCL	100%	100%					
	+ GF	↓					(ITT)			
1996-2001		Cy + GF	*Hist. Subtypes*							
IIL Multictr (14)	(± RT for bulky dis.)	↓	DLBCL	90%	80%		Completed			
Prospective		MTX + VCR	PMBL	6%	10%		Assigned Tx	92%	83%	
Randomized n = 130		↓	Immunoblastic	3%	7%					
Eligible n = 126		VP-16 or DHAP	Anaplastic	1%	3%		Overall CR	70%	59%	
		↓								
Med Age (range)		Mito + Mel	*B symptoms*	55%	70%	**<.05**	TRM	3%	3%	
MegaCEOP 43 y (18-60)		↓								
HDS + Auto 42 y (18-59)		Auto PBSC	*BM Involvement*	27%	22%		6-year FFS	48%	45%	.56

(*Continued*)

Table 2. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Study Design: Protocols by Treatment Group — Control Therapy	Transplant Therapy	Disease Characteristics (at Dx Unless Stated) — Disease Characteristic	Control Group	Transplant Group	*P*	Patient Outcomes — Follow-up (Med, Range) and Pt. Outcomes	Treatment Group — Control (n)	Transplant (n)	*P*
		(± RT for bulky dis.)	*Bulky Disease*	42%	60%	**<.05**	6-year OS	63%	49%	.06
			Risk Factors				Secondary			
			aaIPI ≥3	80%	87%		Neoplasias	0%	3%	
			Stage ≥III	82%	74%					
			LDH ≥Normal	74%	75%		*For aaIPI ≥ 3*			
			>1 Ex-nodal sites	21%	25%		OS	58%	48%	.12
			PS ≥1	56%	63%					
[12] Baldissera 2006	**VACOP-B**	**HDS + Auto PBSCT**		**VACOP-B**	**HDS + Auto PBSCT**		(1.9 y, Not stated)	**VACOP-B**	**HDS + Auto PBSCT**	
			Diagnoses					(27)	(29)	
1−	12× VACOP-B	6× VACOP-B	*de novo*				(ITT)			
		↓	aggressive NHL	100%	100%					
1998-2003	If PD/NR after 6x	Cy + GF					Completed			
GEMOH Multictr (7)	↓	↓	*Hist. Subtypes*			.32	Assigned Tx	70%	62%	
Prospective	Transplant Tx	VP-16	DLBCL	81%	83%					
Randomized n = 56		↓	Other	19%	17%		Overall CR	52%	55%	.80
		BEAM								
Med Age (range)	As rescue for	↓	*B symptoms*	89%	73%	.12	TRM	19%	24%	
VACOP-B 40 y (17-58)	PR/NR after	Auto PBSC								
HDS + Auto 31 y (18-61)	12× VACOB-B		*Bulky Disease*	48%	55%	.60	5-year EFS	47%	30%	.50
	↓	(Salvage chemo per physician)								
	DHAP +		*Risk Factors*				5-year OS	47%	40%	.80
	Cy + VP-16		IPI = High Risk	59%	27%	**.02**				
	+ BEAM + Auto		Stage ≥III	100%	90%	.21				
			LDH >Normal	85%	87%	.78				
	(Salvage chemo per physician)		≥2 Ex-nodal sites	22%	20%	.78				
			PS ≥2	45%	31%	.58				
ORIGINAL DLBCL EBR PHASE III STUDY										
SEQUENTIAL CHEMO VERSUS AUTOLOGOUS BMT AFTER CR TO INDUCTION THERAPY										
[13] Haioun 2000	**Sequential Chemo**	**Auto BMT**		**Sequential Chemo**	**Auto BMT**	All >.05	(8 y, Not stated)	**Sequential Chemo**	**Auto BMT**	
(Final analysis of [14, 15])			*Diagnoses*					(111)	(125)	
1+	MTX	MTX	*de novo* poor risk				(ITT)			
	↓		aggressive NHL	100%	100%					
	Ifo + VP-16	CBV					Completed			
1987-1993	↓		*Hist. Subtypes*				Assigned Tx	100%	69%	
GELA LNH87-2	L-Asparaginase	Auto BM	DLBCL	61%	63%					
Multictr (35)	↓		Immunoblastic	13%	11%		8-year DFS	39%	55%	**.02**
Registered n = 1043	Ara-C		Small uncleaved	5%	6%			CI 29%-49%	CI 46%-64%	

(*Continued*)

Table 2. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Study Design: Protocols by Treatment Group — Control Therapy	Study Design: Protocols by Treatment Group — Transplant Therapy	Disease Characteristics (at Dx Unless Stated) — Disease Characteristic	Control Group	Transplant Group	*P*	Patient Outcomes — Follow-up (Med, Range) and Pt. Outcomes	Treatment Group — Control (n)	Treatment Group — Transplant (n)	*P*
High risk n = 451			Follicular	3%	2%					
Achieved CR n = 277			Lymphoblastic	2%	2%		8-year OS	49%	64%	**.04**
Randomized n = 236			Other	16%	16%			CI 39%-59%	CI 55%-73%	
Med Age (range)			*BM Involvement*	34%	26%		Secondary			
41 y (16-55)							Disease	2%	0%	
			Bulky Disease	70%	74%					
			Risk Factors							
			aaIPI ≥3	100%	100%					
			Stage ≥III	93%	91%					
			LDH >Normal	92%	86%					
			≥2 Ex-nodal sites	30%	33%					
			PS ≥2	44%	42%					
ORIGINAL DLBCL EBR PHASE III STUDY										
FIRST-LINE VACOP-B VERSUS VACOP-B + AUTOLOGOUS SCT										
[16] Santini 1998	**VACOP-B**	**VACOP-B + Auto BMT**		**VACOP-B**	**VACOP-B + Auto BMT**	Not stated	(3.5 y, Not stated)	**VACOP-B**	**VACOP-B + Auto BMT**	
1+			*Diagnoses*					(61)	(63)	
	12× VACOP-B	12× VACOP-B	*de novo* poor risk aggressive NHL	100%	100%					
1991-1995	(DHAP ± RT for salvage)	BEAM					(ITT)			
NHLCSG Multictr (16)			*Hist. Subtypes*							
Prospective		Auto BM + GF	DLBCL	60%	65%		Completed			
Randomized n = 124		± RT	Immunoblastic	20%	21%		Assigned Tx	100%	71%	
			Anaplastic	12%	8%					
Med Age (range)		(DHAP ± RT for salvage)	Unclassifiable	8%	6%		Overall CR	75%	73%	>.05
VACOP-B 45 y (18-59)										
VACOP-B + Auto SCT			*B symptoms*	41%	52%		TRM	7%	6%	
40 y (16-60)										
			Bulky Disease	49%	65%		6-year PFS	48%	60%	.40
								CI 33%-61%	CI 48%-72%	
			Risk Factors							
			aaIPI ≥3	59%	54%		6-year OS	65%	65%	.50
			Stage ≥III	71%	65%			CI 50%-79%	CI 53%-77%	
			LDH >Normal	56%	64%					
			>2 Ex-nodal sites	25%	24%		Secondary			
			PS ≥2	15%	19%		disease	2%	0%	

(*Continued*)

Table 2. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Study Design: Protocols by Treatment Group — Control Therapy	Study Design: Protocols by Treatment Group — Transplant Therapy	Disease Characteristics (at Dx Unless Stated)				Patient Outcomes: Follow-up (Med, Range) and Pt. Outcomes	Patient Outcomes: Treatment Group — Control (n)	Patient Outcomes: Treatment Group — Transplant (n)	
			Disease Characteristic	Control Group	Transplant Group	*P*				*P*
ORIGINAL DLBCL EBR PHASE III STUDY										
FIRST-LINE CHEMO (MACOP-B) VERSUS HDS THERAPY + AUTOLOGOUS SCT										
[17] Gianni 1997	**MACOP-B**	**HDS + Auto SCT**		**MACOP-B**	**HDS + Auto SCT**		(4.6 y, 1.1-8.6 y)	**MACOP-B**	**HDS + Auto SCT**	
1+			*Diagnoses*					(50)	(48)	
	12× MACOP-B ± RT	Dox + VCR + Pred	DLBCL	100%	100%					
1987—Not stated		↓								
Single Center	If Rel/Prog	Cy + GF	*Bulky Disease*	70%	76%		(ITT)			
Prospective	during Tx	↓								
Registered n = 101	↓	VCR + MTX	*Risk Factors*				Completed			
Randomized n = 98	HDS therapy	↓	aaIPI ≥3	74%	94%		Assigned Tx	100%	100%	
		VP-16 + GF	Stage ≥III	68%	72%					
Med Age (range)		↓	LDH >Normal	74%	78%		Overall CR	70%	96%	**.001**
MACOP-B 35 y (17-60)		TBI + Mel + GF	>2 Ex-nodal sites	70%	78%					
HDS + Auto 34 y (18-59)		or	PS ≥2	68%	87%	**.03**	TRM	6%	8%	
		Mito + Mel + GF								
							7-year EFS	49%	76%	**.004**
		(± RT)								
		↓					7-year OS	55%	81%	.09
		Auto PBSC or BM						CI 36-73%	CI 68%-91%	
		If Rel/Prog during Tx ↓ MACOP-B					Secondary disease	2%	2%	

aaIPI indicates age-adjusted International Prognostic Index; ACVBP, doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone; Allo, allogeneic; APO, doxorubicin/ vincristine/prednisone; Ara-C, cytarabine; Auto, autologous; BEAC, carmustine/etoposide/cyclophosphamide/cytarabine; BEAM, carmustine/etoposide/cytarabine/melphalan; BM, bone marrow; BMT, bone marrow transplantation; CBV, cyclophosphamide/carmustine/etoposide; CEEP, cyclophosphamide/epirubicin/vindesine/prednisone; CEOP, cyclophosphamide/ epirubicin/vincristine/prednisone; Chemo, chemotherapy; CHOEP, CHOP+Etoposide; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CHVmP/BV, cyclophosphamide/doxorubicin/teniposide/prednisone/bleomycin/vincrisine; CI, 95% confidence interval; CR, complete remission; CRu, unconfirmed CR; Cy, cyclophosphamide; DFS, disease-free survival; DHAP, dexamethasone/cytarabine/cisplatin; DLCL, diffuse large cell lymphoma; DLBCL, diffuse large B cell lymphoma; EBR, evidence-based review; ECOG, Eastern Cooperative Oncology Group; ECVBP, epirubicin/cyclophosphamide/vindesine/bleomycin/prednisone; EFS, event-free survival; EORTC, European Organization for Research and Treatment of Cancer; Ex-nodal, extranodal; FFS, failure-free survival; G-CSF, granulocyte-colony stimulating factor; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GEMOH, Grupo de Estudos Multicêntricos em Onco-Hematologia; GF, growth factor; GOELAMS, Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang; HD, high dose; HDS, high-dose sequential chemotherapy; HDT, high-dose therapy; HG, high grade; Hist., histological; HR, high risk or hazard ratio; IG, intermediate grade; Ifo, ifosfamide; IIL, Intergruppo Italiano Linfomi; IPI, International Prognostic Index; ITT, intention to treat; LC, large cell; LDH, lactate dehydrogenase; MACOP-B, methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin; Mel, melphalan; MISTRAL, Multicenter International Studies on the Treatment of Aggressive Lymphomas; Mito, mitoxantrone; MTX, methotrexate; NHLCSG, non-Hodgkin Lymphoma Cooperative Study Group; NR, No response; NRM, nonrelapse mortality; OR, odds ratio; OS, overall survival; PB, peripheral blood; PBSCT, peripheral blood stem cell transplantation; PD, progressive disease; PR, partial remission; PMBL, primary mediastinal B-cell lymphoma; PS, performance status; Ref, reference; RR, relative risk; RT, radiation therapy; SC, stem cell; SCT, stem cell transplantation; Seq., sequential; TBI, total body irradiation; TRM, treatment-related mortality; Tx, treatment or therapy; VACOP-B, etoposide/doxorubicin/cyclophosphamide/vincristine/prednisone/ bleomycin; VCR, vincristine; VP-16, etoposide; y, year.

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

†TRM only stated for all patients, not by treatment arm.

‡Trial closed in 2003 after a planned interim analysis because of lack of potential to detect relevant differences in OS, high toxicity in HDS arm, and new treatment options for this patient population.

Table 3. Autologous SCT versus Nontransplantation Therapy for Patients with DLBCL in Partial Remission

Study Design							Patient Outcomes			
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)				Follow-up (Med, Range) & Pt. Outcomes	Treatment Group		
	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*		Control (n)	Transplant (n)	*P*
ORIGINAL DLBCL EBR – SCT VERSUS NON-SCT FOR PARTIAL RESPONDERS (NO NEW PUBLISHED DATA)										
[18] Verdonck 1995	**CHOP**	**HDT + Auto BMT**		**CHOP**	**HDT + Auto BMT**	Not stated	(3 y, 1.7-7 y)	**CHOP**	**HDT + Auto BMT**	
			Diagnoses					(35)	(34)	
1+	8× CHOP	4× CHOP	NHL in PR	100%	100%					
							(ITT)			
1987-1994		Cy + TBI	*Hist. Subtypes*							
Multictr, Prospective			DLBCL	43%	64%		Completed			
Post-induction PR n = 133		Auto BM	Immunoblastic	20%	20%		Assigned Tx	80%	76%	
Eligible for randomization			Follicular	17%	4%					
n = 106			Unclass. IG or HG	20%	12%		Overall CR	74%	68%	.54
Randomized = 69 (65%)										
			BM Involvement	6%	11%		TRM	0%	6%	
Med Age (range)										
Not stated (15-60 y)			*B symptoms*	32%	44%		4-year EFS	53 ± 9%	41 ± 10%	.43
			Bulky Disease	46%	59%		4-year OS	85 ± 6%	56 ± 10%	.12
			Risk Factors							
			IPI ≥3	44%	44%					
			Stage ≥III	57%	40%					
			LDH >Normal	83%	80%					
			≥2 Ex-nodal sites	14%	15%					
			WHO PS 2-4	6%	9%					

Auto indicates autologous; BM(T), bone marrow (transplantation); CHOP, cyclophosphamide/doxorubicin/vincristine/ prednisone; CR, complete remission; Cy, cyclosphosphamide, DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; HG, high grade; IG, intermediate grade; IPI, International Prognostic Index; ITT, intention to treat; LDH, lactate dehydrogenase; NHL, Non-Hodgkin lymphoma; PR, partial remission; OS, overall survival; TBI, total-body irradiation; TRM, treatment-related mortality; Tx, treatment; WHO, World Health Organization.

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

Table 4. Autologous SCT versus Nontransplantation as Salvage Therapy for DLBCL

Study Design							Patient Outcomes			
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease Characteristics (at Dx Unless Stated)				Follow-up (Med, Range) & Pt. Outcomes	Treatment Group		
	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*		Control (n)	Transplant (n)	*P*
ORIGINAL DLBCL EBR PHASE III STUDY OF AUTOLOGOUS BMT AS SALVAGE THERAPY (NO NEW PUBLISHED DATA)										
[19] Philip 1995	**DHAP**	**HDT + Auto BMT**		**DHAP**	**HDT + Auto BMT**	Not stated	(5.25 y, Not stated)	**DHAP**	**HDT + Auto BMT**	
			Diagnoses					(54)	(55)	
1+	6× DHAP	2× DHAP	IG or HG NHL in chemosensitive				(ITT)			
1987-1994	(± RT for bulky dis.)	BEAC	relapse	100%	100%					
PARMA Multictr (51)							Completed			
Prospective		(± RT for bulky dis.)	*Hist. Subtypes*				Assigned Tx	Not stated	89%	
Enrolled n = 215			DLBCL	65%	75%					
Randomized n = 109		Auto BM	Immunoblastic	22%	18%		Overall CR	44%	84%	
			Lymphoblastic	4%	0%					
Med Age (range)			Indolent	9%	7%		TRM	0%	6%	
43 y (18-60)										
			Bulky Disease	41%	29%		5-year EFS	12%	46%	**.001**
			LDH >Normal	39%	36%		5-year OS	32%	53%	**.038**

Auto indicates autologous; BEAC, carmustine/etoposide/cyclophosphamide/cytarabine; BM(T), bone marrow (transplantation); CR, complete remission; DHAP, dexamethasone/ cytarabine/cisplatin; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; HG, high grade; IG, intermediate grade; ITT, intention to treat; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; OS, overall survival; RT, radiation therapy; TRM, treatment-related mortality; Tx, treatment.

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

Table 5. Noncomparative Studies of Autologous SCT as Salvage for Patients ≥60 Years

Study Design				Patient Outcomes	
(Ref #),Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (Range)] & Patient Outcomes	
UPDATE DATA (POST-2000 STUDIES)					
[20]	Prior Ritux therapy (33%)	*Diagnoses*		[1 y (Not stated)]	
Jantunen 2008		DLBCL	100%		
	BEAM (73%)				
2+		*Status at SCT*		3-year NRM	10.8%
	TBI in conditioning (1.1%)	CR1	23%		
2000-2005		CR ≥2 or PR	71%	3-y Relapse	38%
EBMTR Multictr (525)	Auto (99% PBSCT)	Untested or refractory	6%		
Retrospective				3-year PFS	51%
Pts ≥ 60 years n = 463		*Prior Chemo Reg* ≥2	76%		
				3-year OS	60%
Med Age (range) 63 y (60-74)		*Med Dx to SCT*	1.2 y		
		Bulky Disease	19%		
		B Symptoms	43%		
		Risk Factors			
		Stage ≥III	72%		
		LDH >normal	48%		
		PS ≥2	4%		
[21]	*HDT:* BEAC or BEAM	*Diagnoses*		[1.2 y (.1 – 7.3 y)]	
Buadi 2006		NHL	100%		
	Auto (74% PBSCT)				
2+		*Hist. Subtypes*		CR/CRu	89%
		DLBCL	61%		
1995-2003		Transformed FL	26%	TRM	5.4%
Single Center		MC	7%		
Retrospective		T cell	4%	4-year EFS	38%
n = 93		Other	2%		
				4-year OS	38%
Med Age (range) 66 y (60-76.5)		*Status at SCT*			
		CR1	5%		
		PR1	7%		
		CR2 or PR2	54%		
		CR or PR >2	31%		
		Refractory	3%		
		aaIPI ≥2	18%		
[22]	*Prior Chemo*	*Diagnoses*		[1.75 y (Not stated)]	
Jantunen 2006	CHOP (77%)	NHL	100%		
2+	*SC Mobilization*	*Hist. Subtypes*		DLBCL Only	
	Cy + GF (56%)	DLBCL	33%		
2000-2005	or Disease-specific chemo + GF	MC	31%	100-d TRM	10%
Retrospective Multictr (6)		FL	17%		

(*Continued*)

Table 5. (*Continued*)

Study Design				Patient Outcomes	
(Ref #),Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (Range)] & Patient Outcomes	
Analyzed n = 88	*HDT*	T cell	14%	5-year OS	38%
DLBCL n = 29 (33%) (Stratified)	BEAC or BEAM ± GF	Other	5%		
Med Age (range) 63 *y* (60-70)		All Patients			
	Auto PBSCT	*Status at SCT*			
		CR1 or PR1	60%		
		CR or PR ≥2	38%		
		Refractory	2%		
		Med Chemo Reg (range)	7 (3-19)		
		Med Dx to SCT (range)	.75 y (.3-14.6 y)		
		IPI ≥3	50%		

aaIPI indicates age-adjusted International Prognostic Index; Auto, autologous; BEAC, bleomycin/etoposide/doxorubicin/cyclophosphamide; BEAM, carmustine/etoposide/cytarabine/melphalan; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete remission; CRu, unconfirmed complete remission; Cy, cyclosphosphamide; DLBCL, diffuse large B cell lymphoma; Dx, diagnosis; EFS, event-free survival; FL, follicular lymphoma; GF, growth factor; HDT, high-dose therapy; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MC, mantle cell; PBSCT, peripheral blood stem cell transplantation; PFS, progression-free survival; PR, partial remission; PS, performance status; Ritux, rituximab; OS, overall survival; SCT, stem cell transplantation; TBI, total-body irradiation; TRM, treatment-related mortality; Tx, treatment.
*Quality and strength of evidence definitions are listed in Table 1.

To briefly summarize, the quality (see Appendix A, Table 1) of the 11 new studies ranged from 1++ to 1−. Gisselbrecht et al. [4] reported a significant improvement with full-course chemotherapy versus abbreviated chemotherapy + autologous SCT on 5-year event-free survival (EFS) and overall survival (OS), but only for low- to intermediate-risk patients (age-adjusted International Prognostic Index [aaIPI] score ≤2). Milpied et al. [8] reported a significant positive impact of abbreviated chemotherapy + autologous SCT versus full-course chemotherapy on 5-year EFS, but only for intermediate-high to high-risk patients (aaIPI ≥3). The remaining seven studies [5-7,9-12] found no significant differences in outcomes between the autologous SCT and nontransplantation groups. Both meta-analyses [2,3] of published evidence reported that first-line autologous SCT did not consistently provide benefits in OS or EFS when compared with conventional chemotherapy overall or in patients with a low IPI score. The evidence for high IPI score patients was inconclusive because of conflicting results.

Of the three randomized studies from the original DLBCL EBR, Haioun et al. [13] reported a statistically significant advantage in 8-year DFS and OS, and Gianni et al. [17] reported an advantage in 7-year EFS (OS approached significance), for patients who underwent autologous SCT versus nontransplantation therapy. Santini et al. [16] reported a better 6-year DFS rate among patients who underwent autologous SCT versus nontransplantation therapy, but the difference was not statistically significant.

Autologous SCT versus Nontransplantation for Patients in Partial Remission

There are no new randomized studies on the efficacy of autologous SCT versus chemotherapy for patients in partial remission following first-line induction therapy for DLBCL. One Phase III study by Verdonck et al. [18] from the original EBR compared the use of autologous SCT versus chemotherapy (CHOP) as treatment for patients in partial remission after three cycles of first-line chemotherapy and found no significant differences in OS or EFS between the two treatment groups. Table 3 presents the details of the study design and outcomes according to the new format and grading criteria.

Autologous SCT versus Nontransplantation as Salvage Therapy

The 1995 PARMA trial discussed in the original DLBCL EBR remains the only randomized trial comparing autologous SCT versus salvage chemotherapy to date; details of the study design and outcomes are presented in Table 4 according to the new format and grading criteria [19]. The study reported a significantly superior OS and EFS in patients who underwent salvage autologous SCT. Based on this study,

autologous SCT has become the standard of care in patients <60 years with chemosensitive relapsed or primary refractory aggressive non-Hodgkin lymphoma (NHL).

AUTOLOGOUS SCT FOR PATIENTS ≥60 YEARS OF AGE

The PARMA trial [19] did not enroll patients over 60 years, and there are no comparative data of autologous SCT versus nontransplantation as salvage therapy in this patient group. There are three cohort studies [20-22] published since the original review of autologous SCT as salvage therapy for patients ≥60 years. Because of the prognostic importance of age, these noncomparative studies are included in the main article. Table 5 summarizes the study designs, patient populations, and outcomes from these noncomparative studies as evidence on the use of autologous SCT as salvage for patients ≥60 years of age.

AUTOLOGOUS VERSUS ALLOGENEIC SCT

It was noted in the original DLBCL EBR that there were comparative studies of autologous versus allogeneic SCT in NHL patients that would have provided much needed evidence in this area, but they were not included in the EBR because they did not report the proportion of DLBCL patients in their study populations. Presented in this update are two nonrandomized studies published since 2000 that compared the outcomes of autologous versus myeloablative allogeneic SCT as treatment specifically for DLBCL patients. The quality ratings of these studies were 2++ and 2+. Table 6 summarizes the study designs, patient populations, and outcomes from this new evidence. Lazarus et al. [23] reported that allogeneic SCT patients had significantly worse 1-year probabilities of OS, progression-free survival (PFS), and treatment-related mortality (TRM) compared to autologous SCT patients, but the differences were not significant at 3 or 5 years. Aksentijevich et al. [24] reported a significantly worse 3-year TRM for allogeneic compared to autologous SCT patients, but no difference in survival outcomes. Neither study reported a significant difference in risk of relapse or disease progression between the two treatment groups at any time interval.

AUTOLOGOUS SCT

The autologous SCT section of this DLBCL update is composed of 15 comparative and 36 noncomparative studies. The original DLBCL EBR contained no studies that examined the impact of rituximab therapy in combination with autologous SCT. Published since 2000 were 10 comparative studies examining the use of rituximab as part of autologous SCT, including two randomized trials and eight cohort studies. Rituximab has changed the biology of relapsed DLBCL by improving the cure rate after induction therapy, but may result in relapsed disease that is more resistant to salvage therapy. Because rituximab is now the standard of care in the therapy of DLBCL, studies on the use of rituximab prior to autologous SCT are not useful for making treatment recommendations, but may help determine post-autologous SCT prognosis.

Comparative Studies of Autologous SCT

Table 7 presents the study designs and outcomes of three comparative studies used to make treatment recommendations on: autologous BMT versus autologous PBSCT [25], the use of rituximab after autologous SCT [26], and fewer versus more courses of induction therapy prior to autologous SCT [27]. These studies, whose quality ratings ranged from 1++ to 2, are briefly summarized later.

Appendix B (online only) presents the details of the 12 comparative studies of autologous SCT that were not used in the development of the treatment recommendations because of the obsolete or peripheral nature of their findings. These included nine studies of rituximab use prior to, or before and after, autologous SCT [32-40], timing of transplantation [41], intensity of stem cell mobilization regimen [42], and the use of oral versus intravenous busulfan as high-dose therapy prior to autologous SCT [43].

Autologous bond marrow transplantation (BMT) versus peripheral blood stem cell transplantation (PBSCT)

A randomized study by Vose et al. [25], published after the original EBR, compared autologous PBSCT versus BMT as treatment for aggressive non-Hodgkin lymphoma (NHL) patients (61% DLBCL). The quality rating of this study is 1++. Patients who underwent autologous PBSCT had a significantly longer OS, but not EFS, compared to autologous BMT patients.

Rituximab as maintenance therapy after autologous SCT

Whether to use rituximab as routine maintenance therapy post-SCT remains an important clinical question. A study by Haioun et al. [26] reported no significant difference in EFS among patients who received maintenance rituximab therapy versus those who did not.

Fewer versus more cycles of induction therapy prior to first-line autologous SCT

Van Imhoff et al. [27] investigated the impact of three courses of intensified CHOP versus no CHOP prior to two cycles of induction followed by first-line autologous SCT for patients with *de novo* aggressive NHL, and found that patients who received the

Table 6. Autologous versus Allogeneic SCT as First-Line or Salvage Therapy for DLBCL

Study Design							Patient Outcomes			
	Protocols by Treatment Group		Disease (at Dx unless stated) and Transplant Characteristics					Treatment Group		
[Ref #], Quality & Strength of Evidence*, and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) & Pt. Outcomes	Control (n)	Transplant (n)	*P*
UPDATE DATA (POST-2000 STUDIES)										
[23]	**Auto SCT**	**(Myeloablative) Allo SCT**		**Auto SCT**	**Allo SCT**		**Auto** (5 y, .08 - 10.8 y)	**Auto SCT** (837)	**Allo SCT** (79)	
Lazarus 2010			*Diagnoses*							
	BEAM/similar (61%)	TBI + Cy (52%)	DLBCL	100%	100%		**Allo**			
2++	TBI-based (18%)	Bu + Cy (30%)					(6.75 y,1.2-10 y)			
	CBV/similar (10%)	Other (18%)	*Disease Status at SCT*			**<.001**				
1995-2003	Other (11%)		Primary Induct Failure	29%	51%		3-year TRM	16%	43%	>.05
CIBMTR Multictr (156)			CR1	18%	7%			CI 14%-19%	CI 32-51%	
Retrospective	BM (9%)	BM (37%)	≥CR2	17%	8%					
n = 916		HLA-identical sibling	Relapsed- sensitive	29%	18%		3-year PFS	47%	24%	>.05
			Relapsed - resistant	7%	16%			CI 43%-50%	CI 15%-34%	
Med Age (range)										
Auto 48 y (18-60)			*BM Involvement*	17%	42%	**<.001**	3-year OS	53%	26%	>.05
Allo 46 y (21-59)								CI 49%-56%	CI 17%-36%	
(***P* = .05**)			*B symptoms*	46%	58%	**.04**				
							3-year Relapse	40%	33%	>.05
			Med Dx to SCT	1.1 y	.92 y	**.03**		CI 36%-43%	CI 23%-43%	
			(range)	(.17-23.9 y)	(1.7-13 y)					
			Prior Chemo Reg >2	41%	51%	.12				
			Risk Factors							
			aaIPI ≥3	52%	71%	**.02**				
			Stage ≥III	66%	80%	**.003**				
			≥2 Ex-nodal sites	57%	70%	**.02**				
			Karnofsky PS <90	36%	44%	.18				
[24]		**(Myeloablative)**		**Auto**	**Allo**					
Aksentijevich 2006	**Auto SCT**	**Allo SCT**		**SCT**	**SCT**		**Auto** (5.2 y,1.1-16.6 y)	**Auto SCT** (138)	**Allo SCT** (45)	
			Diagnoses							
2+	TBI + Cy (66%) Bu + Cy (25%)	TBI + Cy (38%) Bu + Cy (49%)	DLBCL	100%	100%		**Allo**			
1985-2001	BuCy + VP-16 (9%)	BuCy + VP-16 (13%)	*Disease Status at SCT*			**.004**	(4.2 y,1.2-14 y)			
Single Center			Sensitive	51%	29%					
Retrospective	4-HC purged (59%) BM	T cell-depleted BM	Resistant	49%	71%					
n = 183	or PBSC	HLA-matched sibling								
			B symptoms	23%	36%	.08	3-year TRM	23.9%	51.1%	**.001**
Med Age (range)										
Auto 45 y (18-67)			*Med Dx to SCT*	1 y	.96 y	.70	3-year EFS	30.9%	19.1%	.20
Allo 36 y (18-59)			(range)	(.1-10.7 y)	(.3-6.5 y)					
(***P* < .001**)							3-year OS	33.1%	23.7%	.17

(*Continued*)

Table 6. (*Continued*)

Study Design								Patient Outcomes			
	Protocols by Treatment Group		Disease (at Dx unless stated) and Transplant Characteristics					Treatment Group			
[Ref #], Quality & Strength of Evidence*, and Patient Population	Control Therapy	Transplant Therapy	Disease Characteristic	Control Group	Transplant Group	*P*	Follow-up (Med, Range) & Pt. Outcomes	Control (n)	Transplant (n)	*P*
			Avg.# Chemo Reg	1.9	2.1	.02	3-year Relapse	48.1%	55%	.85
			Stage ≥III	61%	38%	.02				

4-HC indicates 4-hydroperoxycyclophosphamide; aaIPI, age-adjusted International Prognostic Index; Allo, allogeneic; Auto; autologous; BEAM, carmustine/etoposide/ cytarabine/melphalan; BM(T), bone marrow (transplantation); Bu, busulfan; CBV, cyclophosphamide/carmustine/etoposide; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; Cy, cyclosphosphamide; DLBCL, diffuse large B cell lymphoma; Dx, diagnosis; EFS, event-free survival; HLA, human leukocyte antigen; PFS, progression-free survival; PS, performance status; OS, overall survival; SCT, stem cell transplantation; TBI, total-body irradiation; TRM, treatment-related mortality; Tx, treatment; VP-16, etoposide.
*Quality and strength of evidence definitions are listed in Table 1.

intensified CHOP had significantly better OS and EFS than those who did not.

Noncomparative Studies of Autologous SCT

The 36 noncomparative cohort studies included in this update examined the use of autologous SCT as first-line (11 studies) or salvage (25 studies) therapy for DLBCL [44-77].

The design, methodology, and outcomes data from these studies are summarized in Appendix C (online only). These studies represented nonrandomized single- or multi-institutional experiences with autologous SCT or retrospective analyses of transplantation registry data. The quality ratings of the noncomparative autologous SCT studies ranged from 2++ to 2−. Collectively, the outcomes data from these studies contribute to the overall understanding of the effectiveness of autologous SCT in the treatment of DLBCL. One treatment recommendation was developed from several noncomparative Phase II studies on the use of tandem or multiple autologous SCTs [44-47].

ALLOGENEIC SCT

There were no comparative studies in the original EBR, which examined reduced intensity conditioning (RIC) versus myeloablative (MA) conditioning for allogeneic SCT. There is one comparative and five noncomparative allogeneic SCT studies published since 2000 included in this update. Rodriguez et al. [28] reported that patients who received RIC versus MA conditioning prior to allogeneic SCT had significantly higher relapse rates, but no difference in OS or PFS. The quality of this study was a 2+, and Table 8 presents a detailed summary of the study design and outcomes.

Appendix D (online only) summarizes the five noncomparative studies published since the original review, which reported treatment outcomes after either MA (n = 1) or RIC (n = 4) prior to allogeneic SCT [78-82]. The study quality ratings ranged from 2++ to 2+. These studies represent nonrandomized single- or multi-institutional experiences with allogeneic SCT or retrospective analyses of transplantation registry data. Although they contribute to the overall understanding of the effectiveness of allogeneic SCT in the treatment of DLBCL, as noncomparative studies they were not used for making a treatment recommendation regarding conditioning intensity for allogeneic SCT.

AREAS OF NEEDED RESEARCH AND ONGOING STUDIES

After reviewing the updated evidence on the use of SCT for DLBCL, the expert panel identified several important areas of needed research. As noted, some identified areas of needed research are being investigated by

Table 7. Comparative Studies of Autologous SCT for DLBCL

Study Design						Patient Outcomes			
		Disease (at Dx unless stated) and Transplant Characteristics				Treatment Groups			
[Ref #], Quality & Strength of Evidence*, and Patient Population	Protocols by Treatment Group	Disease Characteristic	Treatment Groups	P	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	P
UPDATE DATA (POST-2000 STUDIES)								
AUTOLOGOUS BMT VERSUS PBSCT								
[25]			**Auto BMT**	**Auto PBSCT**		(4.6 y, 2.6-7.0 y)	**Auto BMT**	**Auto PBSCT**	
Vose, 2002	**Auto BMT**	**Auto PBSCT**					(46)	(47)	
			Diagnoses						
1++	BEAC	BEAC	Aggressive NHL	100%	100%				
		+ GF for mobilization				(ITT)			
1993-1997			*Hist. Subtypes*			>.05			
Multicenter (5)	Auto BMT	Auto PBSCT	DLBCL	61%	62%		Overall CR	54%	72%	.09
Enrolled n=105	followed by GF	followed by GF	Immunoblastic	22%	17%					
Randomized n=93			Composite	6%	13%		4-year EFS	37%	37%	.39
			Unclassified	11%	8%			CI 23%-51%	CI 23%-51%	
Med Age (range)										
BMT 44 y (18-69)			*Disease Status at SCT*			>.05	4-year OS	43%	61%	**.037**
PBSCT 49 y (22-72)			PIF/Rel Sensitive	60%	64%			CI 29%-58%	CI 47%-75%	
(*P* >.05)			PIF/Rel Resistant	7%	9%					
			CR1	9%	9%					
			CR2	13%	12%					
			Untreated Relapse	11%	6%					
			Prior Chemo Reg >2	13%	32%	**.046**				
			Bulky disease	7%	6%	>.05				
			Risk Factors							
			Stage ≥III	53%	60%	>.05				
			LDH >Normal	26%	30%	>.05				
			High Risk	15%	13%	>.05				
RITUXIMAB VERSUS NO RITUXIMAB MAINTENANCE AFTER AUTOLOGOUS SCT FOR *DE NOVO* DLBCL									
[26]	**No Ritux**	**Ritux**		**No Ritux**	**Ritux**	All		No Ritux	Ritux	
Haioun 2009			*Diagnoses*			>.05	(4 y, Not stated)	(130)	(139)	
	Randomized Induction	*Randomized Induction*	*Aggressive* DLBCL	100%	100%					
1+	ACVBP or AC/ACE	ACVBP or AC/ACE								
			BM Involvement	24%	24%		2-year EFS	71%	80%	.099
1999-2004	*HDT*	*HDT*						CI 62%-78%	CI 72%-86%	
Multictr (40)	Mito + Cy + VP-16	Mito + Cy + VP-16	*Bulky disease*	36%	40%					
Enrolled n = 476	+ Carmustine	+ Carmustine								
SCT eligible n = 402			*Risk Factors*							
2nd Randomization n = 269	Auto SCT	Auto SCT	aaIPI ≥3	100%	100%					

(*Continued*)

Table 7. (*Continued*)

[Ref #], Quality & Strength of Evidence*, and Patient Population	Protocols by Treatment Group		Disease (at Dx unless stated) and Transplant Characteristics: Disease Characteristic	Treatment Groups		P	Follow-up (Med, Range) & Pt. Outcomes	Treatment Groups (n)	(n)	P
			Stage ≥III	97%	97%					
Med Age (range)	2nd randomization to observation	2nd randomization to 4x Ritux	≥2 Ex-nodal sites	66%	60%					
No Ritux 47 y (18-59)										
Ritux 47 y (19-59)			LDH >Normal	93%	95%					
			PS ≥2	35%	29%					
FEWER VERSUS MORE CYCLES OF INDUCTION THERAPY PRIOR TO FIRST-LINE AUTOLOGOUS SCT										
[27]	**No CHOP**	**CHOP**		**No CHOP**	**CHOP**		**No CHOP**	**No CHOP**	**CHOP**	
Van Imhoff 2005	**(HOVON-27)**	**(HOVON-40)**		**(HOVON-27)**	**(HOVON-40)**		(6.9 y, 4.2-9.3 y)	**(HOVON-27)** (66)	**(HOVON-40)** (81)	
2++		3× CHOP	*Diagnoses*				**CHOP**			
			de novo aggress. NHL	100%	100%		(2.8 y, 1.1-4.9 y)			
1994-1999	*HDS Therapy*	*HDS Therapy*								
HOVON-27 trial	Cy + Dox + Pred	Cy + Dox + Pred	*Hist. Subtypes*			.54				
1999-2001	+ GF	+ GF	DLBCL	76%	83%		TRM	9%	6%	
HOVON-40 trial	↓	↓	FL	9%	4%					
Multictr	VP-16 + Mito + Pred	VP-16 + Mito + Pred	Anaplastic LCL	9%	5%		4-year EFS	15%	49%	**<.001**
Retrospective	+ GF	+ GF	T cell	5%	6%			CI 8%-25%	CI 38%-59%	
Total n = 395			Unclassified	2%	2%					
	HDT	*HDT*					4-year OS	21%	50%	**.007**
Med Age (range)	BEAM	BEAM	*B Symptoms*	79%	81%	.68		CI 12%-32%	CI 37%-61%	
No CHOP 49 y (15-64)										
CHOP 52 y (18-65)	Auto PBSCT	Auto PBSCT	*Bulky Disease*	45%	33%	.17				
(*P* = .62)	± RT	± RT								
			Risk Factors							
			aaIPI ≥2	100%	100%					
			Stage ≥III	100%	100%					
			LDH ≥ Normal	98%	100%					
			>1 Ex-nodal sites	47%	32%	.13				
			PS ≥2	35%	20%	**.04**				

aaIPI indicates age-adjusted International Prognostic Index; Ara-C, cytarabine; Auto; autologous; BEAC, carmustine/etoposide/cyclophosphamide/cytarabine; BEAM, carmustine/etoposide/cytarabine/melphalan; BMT, bone marrow transplantation; Bu, Busulfan; CBV, cyclophosphamide/carmustine/etoposide; CHOP, cyclophophamide/ doxorubicin/vincristine/prednisone; CI, 95% confidence interval; CR, complete remission; Cy, cyclosphosphamide; DLBCL, diffuse large B cell lymphoma; Dox, doxorubicin; Dx, diagnosis; EFS, event-free survival; ESHAP, etoposide/cytarabine/methylprednisolone/cisplatin; FL, follicular lymphoma; GF, growth factor; HDS, high-dose sequential therapy; HDT, high-dose therapy; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; HR, high risk; IPI, International Prognostic Index; IV, Intravenous; LDH, lactate dehydrogenase; mAbs, monoclonal antibodies; MC, mantle cell; Mito, mitoxantrone; NHL, non-Hodgkin Lymphoma; PBSCT, peripheral blood stem cell transplantation; PFS, progression-free survival; PIF, primary induction failure; PR, partial remission; Pred, prednisone; PS, performance status; OS, overall survival; R or Ritux, rituximab; RT, radiation therapy; SCT, stem cell transplantation; TBI, total-body irradiation; TILC, time interval since last chemotherapy; TRM, treatment-related mortality; Tx, treatment, VP-16, etoposide.
*Quality and strength of evidence definitions are listed in Table 1.

Table 8. Comparative Study of Allogeneic SCT for DLBCL

Study Design						Patient Outcomes			
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group	Disease (at Dx unless stated) and Transplant Characteristics				Follow-up (Med, Range) & Pt. Outcomes	Treatment Groups		
		Disease Characteristic	Treatment Groups		*P*		(n)	(n)	*P*
UPDATE DATA (POST-2000 STUDY)									
MYELOABLATIVE VERSUS REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC SCT									
[28]	**CMR**	**RIC**		**CMR**	**RIC**		**CMR**	**CMR**	**RIC**
Rodriguez 2006							(5.8 y, 2.8-8.1 y)	(48)	(40)
	Conditioning	*Conditioning*	*Diagnoses*						
2+	f-TBI + Cy (85%) or Bu + Cy (15%)	Flu + Mel	NHL	100%	100%		**RIC** (1.7 y, .5-3.5 y)		
1991-2000—CMR Pts.			*Hist. Subtypes*						
2000-2003—RIC Pts.	*Donors*	*Donors*	Low grade B cell	33%	30%				
Single Center	MUD (17%)	MUD (43%)	Intermed grade B cell	38%	40%		Overall		
Retrospective			(including DLBCL &				1-year TRM	0%	6%
Total n = 88	*SC Source*	*SC Source*	transformed DLBCL)						
Int. grade B cell n = 28	PBSC (33%)	PBSC (90%)	Mantle cell	21%	13%		Int Grade Only		
(Stratified)			T cell	8%	17%		2-year PFS	44%	31%	.18
	Allo SCT	Allo SCT							
Med Age (range)			*Prior Auto SCT*	10%	40%	**.002**	2-year OS	50%	36%	.56
CMR 44 y (18-54)									
RIC 51 y (20-67)			*Med Prior Chemo Reg*	3	2	**.02**	2-year Relapse	12%	44%	**.02**
			Chemosensitive at SCT	50%	78%	**.007**			

Allo indicates allogeneic; Auto, autologous; Bu, busulfan; Chemo, chemotherapy; CMR, conventional myeloablative regimens; CR, Complete remission; Cy, cyclosphosphamide, DLBCL, diffuse large B cell lymphoma; Flu, fludarabine; f-TBI, fractionated total-body irradiation; Mel, melphalan; MUD, matched unrelated donor; NHL, Non-Hodgkin lymphoma; PBSC, peripheral blood stem cells; PFS, progression-free survival; RIC, reduced-intensity conditioning; OS, overall survival; SCT, stem cell transplantation; TRM, treatment-related mortality.
*Quality and strength of evidence definitions are listed in Table 1.

new trials or ongoing studies that are currently accruing patients, maturing follow-up, or have been published in abstract form. None of the data described below was used as evidence for the review or for making treatment recommendations. This section is provided for the reader's information only.

Induction

• Identify more effective induction regimens to optimize disease response and reduce the need for autologous SCT.

There are no ongoing studies that address this area of needed research.

• Identify and examine the efficacy of predictive tests (ie, PET scanning) to classify patients who are at high risk for early treatment failure (those who are primary refractory to initial therapies and those who respond but quickly relapse) and candidates for autologous SCT.

Trneny et al. [29] prospectively recorded the PET scans at the end of induction treatment in 123 patients with relapsed or refractory DLBCL enrolled in the CORAL study. PET was negative in 61 patients and positive in 62. Of these, 60 and 58 patients completed three cycles of RICE or RDHAP, with 50 PET− and 26 PET+ patients receiving BEAM + autologous SCT. Intent-to-treat analysis found a significant improvement in for 3-year EFS (40% versus 16%, $P < .0001$) and 3-year OS (66% versus 49%, $P = .007$) for PET− and PET+ patients, respectively. For patients who underwent autologous SCT, there was a significant improvement in EFS ($P = .03$) for PET−, but no signficant difference in PFS or OS.

• Update the IPI to include molecular markers and/or gene expression profiling to better discriminate prognostic groups that would benefit from SCT.

There are no ongoing studies that address this area of needed research.

• Determine the potential benefit of first-line autologous SCT for patients with central nervous system involvement.

There are no ongoing studies that address this area of needed research.

Salvage after Induction Failure

• Identify effective salvage regimens to optimize disease response prior to autologous SCT.

Gisselbrecht et al. [30] presented the preliminary intent-to-treat analysis of 396 patients enrolled in the ongoing multicenter intergroup Phase III Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, which began in 2003 in 11 countries and investigated the choice of salvage therapy in refractory or relapsed DLBCL. Patients were randomized to receive three cycles of RICE or RDHAP, and responders were treated by autologous SCT with BEAM. Autologous SCT was performed in 206 patients. No difference was found between RICE and RDHAP in response rate (63.5%, confidence interval [CI] 56%-70% versus 62.8%, CI 55%-69%) or 3-year EFS (26% versus 35%, $P = .60$). Three-year EFS was negatively affected by prior exposure to rituximab versus no exposure (21% versus 47%, $P < .0001$).

At a median follow-up of 27 months, Mounier et al. [31] presented the findings of a GELA Phase II (LNH-2003-3) case-controlled study of the survival benefit of intensive high dose therapy with rituximab + ACVBP followed by BEAM and autologous PBSCT versus ACVBP + autologous PBSCT. From 2004 to 2005, 209 patients received the R+ACVBP regimen and were matched with patients from the LNH-98-3 trial who received the ACVBP regimen. Intent-to-treat 3-year PFS was significantly higher in the R+ACVBP than in the ACVBP arm (75% versus 58%, $P = .0003$), as was the estimated 3-year OS (78% versus 67%, $P = .05$).

High-Dose Therapy Regimens with Autologous SCT

• Identify effective high dose therapy regimens to optimize complete response, improve hematopoietic recovery, and reduce TRM and incidence of secondary disease.

The Bone Marrow Transplant-Clinical Trials Network (BMT-CTN) has sponsored a randomized, Phase III trial (Protocol 0401) that compares the high-dose regimens rituximab + BEAM versus I131-tositumomab + BEAM followed by autologous SCT in adult (18-80 years) patients with persistent or recurrent chemotherapy-sensitive DLBCL. A total of 224 patients have been accrued. The primary outcome measure is PFS, with secondary outcome measures including OS, time to progression, complete response, and partial response at day 100, time to hematopoietic recovery, hematologic function, toxicity, TRM, and incidence of secondary disease.

The M.D. Anderson Cancer Center has sponsored a randomized trial (NCT00472056) comparing standard (375 mg/m^2) versus high-dose (1000 mg/m^2) rituximab + BEAM followed by autologous SCT in adult (up to 80 years) patients with relapsed DLBCL. A total accrual of 100 patients is projected. DFS in the two treatment arms is the primary outcome measure for patients 65 years or younger; DFS and TRM are the outcome measures of interest for patients older than 65 years.

Another M.D. Anderson Cancer Center sponsored randomized trial (NCT00591630) compares 90Y-ibritumomab tiuxetan + BEAM + rituximab versus BEAM + rituximab with or without rituximab maintenance (applicable to next section) after autologous SCT for adult (18-70 years) patients with relapsed, chemotherapy-sensitive DLBCL. A total accrual of 100 patients is projected, and PFS is the primary outcome measure.

Maintenance Therapy After Autologous SCT

• Identify effective maintenance regimens to optimize disease control post-autologous SCT.

The Gisselbrecht et al. CORAL study identified above [30] also investigated the role of rituximab maintenance after autologous SCT. A second randomization after autologous SCT allocated patients to observation or maintenance therapy with rituximab for one year. Longer follow-up is needed for the analysis of this second randomization.

The Eastern Cooperative Oncology Group (ECOG) has sponsored a randomized, multicenter, Phase III trial (NCT00052923) comparing autologous SCT with or without rituximab maintenance for adult (18-70 years) patients with relapsed or progressive DLBCL. A total accrual of 427 patients is projected; OS and TRM are the primary outcome measures.

CureTech Ltd. has sponsored a Phase II, multicenter study (NCT00532259) with Northwestern University investigating the safety and efficacy of the monoclonal antibody CT-011 as maintenance therapy following autologous PBSCT in adult patients (18+ years) with relapsed DLBCL. A total of 70 patients has been accrued; PFS, EFS, OS, and toxicity are the outcome measures of interest.

The Case Comprehensive Cancer Center has sponsored a Phase I/II trial (NCT01045928) investigating the efficacy and best dose of lenalidomide + rituximab as maintenance therapy after autologous SCT for adult (18+ years) patients with B cell NHL, including DLBCL patients. Expected enrollment is 71 patients. Primary outcomes measures are maximum tolerated dose and safety of lenalidomide + rituximab (Phase I) and tolerability of the maintenance therapy (Phase II); a secondary outcome measure is PFS (Phase II).

The University of Nebraska has sponsored a Phase I/II trial (NCT01035463), investigating the efficacy and best dose of lenalidomide as maintenance therapy after combination chemotherapy with or without rituximab and autologous SCT for adult (19+ years) patients with persistent or recurrent NHL that is resistant to chemotherapy. Expected enrollment is 44 patients. Primary outcome measures are maximum tolerated dose and toxicity of lenalidomide (Phase I); secondary outcome measures are OS, EFS, and complete response rate (Phase II).

The Fred Hutchinson Cancer Research Center has sponsored a Phase II trial (NCT00992446) investigating the efficacy and safety of bortezomib and vorinostat as maintenance therapy after autologous SCT in adult (18+ years) patients with NHL, including DLBCL patients. Estimated enrollment is 20 patients, and time to progression and toxicity are the outcome measures of interest.

Salvage after Failed SCT

• Examine the efficacy of reduced intensity allogeneic SCT as rescue after a failed autologous SCT.

There are no ongoing studies that address this area of needed research.

Other Ongoing Studies

The following are ongoing studies that did not relate to any of the areas of needed research suggested by the expert panel, but whose future outcomes may affect treatment recommendations.

Autologous SCT versus Non-SCT Therapy

The Southwest Oncology Group (SWOG) has sponsored a randomized, multicenter, Phase III trial (NCT00004031) comparing the effectiveness of standard CHOP ± R (×8 cycles) versus CHOP ± R (×6 cycles) followed by autologous PBSCT with total body irradiation (TBI)-based regimens for treating adult (15-65 years) patients with diffuse aggressive intermediate/high grade NHL. Patients in the CHOP ± R arm can cross over to the SCT arm at the time of disease progression. The target accrual is 360 patients; OS and PFS are the primary outcome measures.

The British National Lymphoma Investigation has sponsored a randomized, multicenter, Phase III trial (NCT00003578) comparing the effectiveness of high dose chemotherapy alone versus SCT as part of planned initial therapy for adult (16-65 years) patients with poor risk intermediate/high grade NHL, including DLBCL patients. A total accrual of 500 patients is projected.

Reduced-intensity allogeneic SCT as consolidation after autologous SCT

Stanford University and the National Institutes of Health have sponsored a Phase II, non-randomized trial (NCT00482053) investigating a nonmyeloablative conditioning regimen of total lymphoid irradiation and antithymocyte globulin (ATG) followed by an HLA-matched allogeneic SCT as consolidation after autologous SCT in adult (18-70 years) patients with poor risk recurrent or primary refractory DLBCL. The estimated enrollment is 30 patients. Primary outcome measures are EFS and toxicity; OS and TRM are secondary outcome measures.

Nonmyeloablative/RIC for allogeneic SCT

M.D. Anderson Cancer Center has sponsored a single-center study (NCT00880815) investigating the efficacy of a nonmyeloablative regimen of fludarabine, bendamustine, and rituximab as conditioning prior to allogeneic SCT for adult (18-70 years) patients with lymphoid malignancies, including DLBCL patients who are not eligible for autologous SCT and who have an HLA-matched sibling donor. The projected accrual is 46 patients, and the primary outcome measure is maximum tolerated dose and toxicity.

STRENGTHS/LIMITATIONS AND DISCUSSION

The strengths of this updated systematic evidence-based review are the details about each study's design and outcomes conveyed in the summary tables for each major section, and the treatment recommendations made by the DLBCL 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. Except in the Ongoing Studies section, data published in abstract form were not included in this review 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 DLBCL EBR Update is that much of the newly presented data is already obsolete in terms of the current standard of care, stressing the need for more timely updates of the EBRs. For example, an abundance of research on the effectiveness of rituximab prior to autologous SCT has been published since the original DLBCL EBR, but as rituximab is now the current standard of care, these studies are not useful for making treatment recommendations. In addition, the lengthy process of conducting and reporting clinical research emphasizes the need to identify surrogate endpoints or molecular markers that are predictive of long-term survival in DLBCL patients. Further delineation of clinical risk factors may facilitate appropriate selection of DLBCL patients for autologous versus allogeneic SCT.

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REFERENCES

1. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin' lymphoma: a evidence-based review. *Biol Blood Marrow Transplant*. 2001;7: 308-331.
2. Greb A, Bohlius J, Trelle S, et al. High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma: results of a comprehensive meta-analysis. *Cancer Treat Rev*. 2007;33:338-346.
3. Strehl J, Mey U, Glasmacher A, et al. High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis. *Haematologica*. 2003;88:1304-1315.
4. Gisselbrecht C, Lepage E, Molina T, et al. Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. *J Clin Oncol*. 2002;20:2472-2479.
5. Kaiser U, Uebelacker I, Abel U, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. *J Clin Oncol*. 2002;20:4413-4419.
6. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin lymphoma: randomized phase III EORTC Study. *J Natl Cancer Inst*. 2001;93:22-30.
7. Martelli M, Gherlinzoni F, De Renzo A, et al. Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non-Hodgkin lymphoma: an Italian multicenter randomized trial. *J Clin Oncol*. 2003;21:1255-1262.
8. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. *N Engl J Med*. 2004;350:1287-1295.
9. Olivieri A, Santini G, Patti C, et al. Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin lymphoma: long-term results by the NHLCSG. *Ann Oncol*. 2005;16:1941-1948.
10. Betticher D, Martinelli G, Radford J, et al. Sequential high dose chemotherapy as initial treatment for aggressive sub-types of Non-Hodgkin Lymphoma: results of the international randomized phase III trial (MISTRAL). *Ann Oncol*. 2006;17:1546-1552.
11. Vitolo U, Liberati AM, Cabras MG, et al. High dose sequential chemotherapy with autologous transplantation versus dose-dense chemotherapy *MegaCEOP* as first line treatment in poor-prognosis diffuse large cell lymphoma: an "Intergruppo Italiano Linfomi" randomized trial. *Haematologica*. 2005;90:793-801.
12. Baldissera R, Nucci M, Vigorito A, et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin lymphoma patients: a prospective randomized GEMOH report. *Acta Haematol*. 2006;115:15-21.

13. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin lymphoma: final analysis of the prospective LNH87-2 Protocol—a Groupe d'Etude des Lymphomes de l'Adulte study. *J Clin Oncol*. 2000;18:3025-3030.
14. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15:1131-1137.
15. Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1994;12:2543-2551.
16. Santini G, Salvagno L, Leoni P, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. *J Clin Oncol*. 1998;16:2796-2802.
17. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med*. 1997;336:1290-1298.
18. Verdonck LF, van Putten WLJ, Hagenbeek A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin lymphoma. *N Engl J Med*. 1995;332:1045-1051.
19. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin lymphoma. *N Engl J Med*. 1995;333:1540-1545.
20. Jantunen E, Canals C, Rambaldi A, et al. Autologous stem cell transplantation in elderly patients (≥60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry. *Haematologica*. 2008;93:1837-1842.
21. Buadi F, Micallef I, Ansell S, et al. Autologous hematopoietic stem cell transplantation for older patients with relapsed non-Hodgkin lymphoma. *Bone Marrow Transplant*. 2006;37:1017-1022.
22. Jantunen E, Itala M, Juvonen E, et al. Autologous stem cell transplantation in elderly (>60 years) patients with non-Hodgkin lymphoma: a nation-wide analysis. *Bone Marrow Transplant*. 2006;37:367-372.
23. Lazarus HM, Zhang M-J, Carreras J, et al. A comparison of HLA-identical sibling allogeneic versus autologous transplantation for diffuse large B-cell lymphoma: A report from the CIBMTR. *Biol Blood Marrow Transplant*. 2010;16:35-45.
24. Aksentijevich I, Jones R, Ambinder R, Garrett-Mayer E, Flinn I. Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2006;12:965-972.
25. Vose JM, Sharp G, Chan WC, et al. Autologous transplantation for aggressive non-Hodgkin lymphoma: Results of a randomized trial evaluating graft source and minimal residual disease. *J Clin Oncol*. 2002;20:2344-2352.
26. Haioun C, Mounier N, Emile JF, et al. Rituximab versus observation after high-dose consolidative first-line chemotherapy with autologous stem-cell transplantation in patients with poor-risk diffuse large B-cell lymphoma. *Ann Oncol*. 2009;20:1985-1992.
27. van Imhoff GW, van der Holt B, MacKenzie MA, et al. Impact of three courses of intensified CHOP prior to high-dose sequential therapy followed by autologous stem-cell transplantation as first-line treatment in poor-risk, aggressive non-Hodgkin lymphoma: comparative analysis of Dutch-Belgian Hemato-Oncology Cooperative Group Studies 27 and 40. *J Clin Oncol*. 2005;23:3793-3801.
28. Rodriguez R, Nademanee A, Ruel N, et al. Comparison of reduced-intensity and conventional myeloablative regimens for allogeneic transplantation in non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2006;12:1326-1334.
29. Trneny M, Bosly A, Bouabdallah K, et al. Independent predictive value of PET-CT pre-transplant in relapsed and refractory patients with CD20 diffuse large B-cell lymphoma (DLBCL) Included in the CORAL study. *ASH Annual Meet Abstr*. 2009;114:881.
30. Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. *J Clin Oncol*. 2009;27:8509.
31. Mounier N, Gisselbrecht C, Fitoussi O, et al. Benefit of rituximab combined to ACVBP (R-ACVBP) over ACVBP in 209 poor-risk BDLC NHL patients treated with up-front consolidative autotransplantation: a GELA phase II trial (LNH 2003-3). *J Clin Oncol*. 2009;27:8507.
32. Vellenga E, van Putten WLJ, van't Veer MB, et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. *Blood*. 2008;111:537-543.
33. Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL-TAMO study. *Haematologica*. 2008;93:1829-1836.
34. Vitolo U, Chiappella A, Angelucci E, et al. Dose-dense and high-dose chemotherapy plus rituximab with autologous stem cell transplantation for primary treatment of diffuse large B-cell lymphoma at poor prognosis: a phase II multicenter study. *Haematologica*. 2009;94:1250-1258.
35. Fenske TS, Hari PN, Carreras J, et al. Impact of pre-transplant rituximab on survival after autologous hematopoietic stem cell transplantation for diffuse large B cell lymphoma. *Biol Blood Marrow Transplant*. 2009;15:1455-1464.
36. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. 2004;103:3684-3688.
37. Han L, Zhou J, Hirose T, et al. Feasibility and efficacy of high-dose melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) chemotherapy with or without rituximab followed by autologous stem cell transplantation for aggressive and relapsed non-Hodgkin lymphoma. *Int J Hematol*. 2006;84:174-181.
38. Khouri IF, Saliba RM, Hosing C, et al. Concurrent administration of high-dose rituximab before and after autologous stem-cell transplantation for relapsed aggressive B-cell non-Hodgkin lymphomas. *J Clin Oncol*. 2005;23:2240-2247.
39. Tarella C, Zanni M, Magni M, et al. Rituximab improves the efficacy of high-dose chemotherapy with autograft for high-risk follicular and diffuse large B-cell lymphoma: A multicenter Gruppo Italiano Terapie Innnovative nei Linfomi survey. *J Clin Oncol*. 2008;26:3166-3175.
40. Kamezaki K, Kikushige Y, Numata A, et al. Rituximab does not compromise the mobilization and engraftment of autologous peripheral blood stem cells in diffuse large B-cell lymphoma. *Bone Marrow Transplant*. 2007;39:523-527.
41. Holtan SG, Porrata LF, Inwards DJ, et al. Timing of autologous stem cell transplantation from last chemotherapy affects lymphocyte collection and survival in non-Hodgkin lymphoma. *Br J Haematol*. 2006;133:628-633.
42. Damon L, Damon LE, Gaensler K, et al. Impact of intensive PBSC mobilization therapy on outcomes following auto-SCT for non-Hodgkin lymphoma. *Bone Marrow Transplant*. 2008;42:649-657.
43. Aggarwal C, Gupta S, Vaughan WP, et al. Improved outcomes in intermediate- and high-risk aggressive non-Hodgkin lymphoma after autologous hematopoietic stem cell transplantation substituting intravenous for oral busulfan in a busulfan,

cyclophosphamide, and etoposide preparative regimen. *Biol Blood Marrow Transplant*. 2006;12:770-777.
44. Tarella C, Zanni M, Di Nicola M, et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early-intensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). *Leukemia*. 2007;21:1802-1811.
45. Glass B, Kloess M, Bentz M, et al. Dose-escalated CHOP plus etoposide (MegaCHOEP) followed by repeated stem cell transplantation for primary treatment of aggressive high-risk non-Hodgkin lymphoma. *Blood*. 2006;107:3058-3064.
46. Coso D, Sebban C, Boulat O, et al. A phase II trial of rituximab as adjuvant to intensive sequential chemotherapy in patients under 60 years with untreated poor-prognosis diffuse large B-cell lymphoma. *Bone Marrow Transplant*. 2006;38:217-222.
47. Haioun C, Mounier N, Quesnel B, et al. Tandem autotransplant as first-line consolidative treatment in poor-risk aggressive lymphoma: A pilot study of 36 patients. *Ann Oncol*. 2001;12:1749-1755.
48. Haioun C, Gisselbrecht C, Quesnel B, Morel P, Reyes F. Double autotransplant (DAT) as first-line consolidative treatment in poor-risk aggressive lymphoma: A pilot study of 31 patients [abstract]. *Bone Marrow Transplant*. 1998;21(Suppl 1):S174.
49. Mounier N, Gisselbrecht C, Briere J, et al. Prognostic factors in patients with aggressive non-Hodgkin lymphoma treated by front-line autotransplantation after complete remission: A cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2004;22:2826-2834.
50. Arranz R, Conde E, Grande C, et al. Dose-escalated CHOP and tailored intensification with IFE according to early response and followed by BEAM/autologous stem-cell transplantation in poor-risk aggressive B-cell lymphoma: a prospective study from the GEL-TAMO Study Group. *Eur J Haematol*. 2008;80:227-235.
51. Caballero MD, Perez-Simon JA, Iriondo A, et al. High-dose therapy in diffuse large cell lymphoma: results and prognostic factors in 452 patients from the GEL-TAMO Spanish Cooperative Group. *Ann Oncol*. 2003;14:140-151.
52. Papajik T, Raida L, Faber E, et al. High-dose therapy and autologous stem cell transplantation in patients with diffuse large B-cell lymphoma in first complete or partial remission. *Neoplasma*. 2008;55:215-221.
53. Stewart DA, Bahlis N, Valentine K, et al. Upfront double high-dose chemotherapy with DICEP followed by BEAM and autologous stem cell transplantation for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood*. 2006;107:4623-4627.
54. Vranovsky A, Ladicka M, Lakota J. Autologous stem cell transplantation in first-line treatment of high-risk aggressive non-Hodgkin lymphoma. *Neoplasma*. 2008;55:107-112.
55. Bertz H, Zeiser R, Lange W, et al. Long-term follow-up after high-dose chemotherapy and autologous stem-cell transplantation for high-grade B-cell lymphoma suggests an improved outcome for high-risk patients with respect to the age-adjusted International Prognostic Index. *Ann Oncol*. 2004;15:1419-1424.
56. Benjamin JE, Chen GL, Cao TM, et al. Long-term follow-up of patients with diffuse large B-cell non-Hodgkin's lymphoma receiving purged autografts after induction failure. *Bone Marrow Transplant*. 2009;45:303-309.
57. Cortelazzo S, Rambaldi A, Rossi A, et al. Intensification of salvage treatment with high-dose sequential chemotherapy improves the outcome of patients with refractory or relapsed aggressive non-Hodgkin lymphoma. *Br J Haematol*. 2001;114:333-341.
58. Robertson MJ, Abonour R, Hromas R, et al. Augmented high-dose regimen of cyclophosphamide, carmustine, and etoposide with autologous hematopoietic stem cell transplantation for relapsed and refractory aggressive non-Hodgkin lymphoma. *Leuk Lymphoma*. 2005;46:1477-1487.
59. Josting A, Sieniawski M, Glossmann JP, et al. High-dose sequential chemotherapy followed by autologous stem cell transplantation in relapsed and refractory aggressive non-Hodgkin lymphoma: results of a multicenter phase II study. *Ann Oncol*. 2005;16:1359-1365.
60. Alousi A, Saliba R, Okoroji G, et al. Disease staging with positron emission tomography or gallium scanning and use of rituximab predict outcome for patients with diffuse large B-cell lymphoma treated with autologous stem cell transplantation. *Br J Haematol*. 2008;142:786-792.
61. Horwitz SM, Negrin RS, Blume KG, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Blood*. 2004;103:777-783.
62. Hoppe BS, Moskowitz CH, Filippa DA, et al. Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity. *J Clin Oncol*. 2008;26:1858-1864.
63. Vose JM, Rizzo DJ, Tao-Wu J, et al. Autologous transplantation for diffuse aggressive Non-Hodgkin lymphoma in first relapse or second remission. *Biol Blood Marrow Transplant*. 2004;10:116-127.
64. Vose JM, Zhang M-J, Rowlings PA, et al. Autologous transplantation for diffuse aggressive non-Hodgkin lymphoma in patients never achieving remission: A report from the Autologous Blood and Marrow Transplant Registry. *J Clin Oncol*. 2001;19:406-413.
65. Rodriguez J, Caballero MD, Gutierrez A, et al. Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin lymphoma not achieving complete response after induction chemotherapy: the GEL-TAMO experience. *Ann Oncol*. 2004;15:1504-1509.
66. Lerner RE, Thomas W, DeFor TE, Weisdorf DJ, Burns LJ. The International Prognostic Index assessed at relapse predicts outcomes of autologous transplantation for diffuse large-cell non-Hodgkin lymphoma in second complete or partial remission. *Biol Blood Marrow Transplant*. 2007;13:486-492.
67. Sohn BS, Park I, Kim EK, et al. Comparison of clinical outcome after autologous stem cell transplantation between patients with peripheral T-cell lymphomas and diffuse large B-cell lymphoma. *Bone Marrow Transplant*. 2009.
68. Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. 2003;102:1989-1996.
69. Kuruvilla J, Pintilie M, Tsang R, et al. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2008;49:1329-1336.
70. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. *Br J Haematol*. 2003;120:978-985.
71. Kewalramani T, Zelenetz A, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. *Br J Haematol*. 2006;134:202-207.
72. McCoy AG, Smith EP, Atkinson ME, et al. A novel preparative regimen for autologous transplant in non-Hodgkin lymphoma: Long-term experience with etoposide and thiotepa. *Bone Marrow Transplant*. 2004;33:19-24.
73. Usui N, Yano S, Asai O, et al. Long-term follow-up high-dose chemotherapy (drug-only program) followed by autologous stem cell transplantation for aggressive non-Hodgkin lymphomas. *Clin Lymphoma Myeloma*. 2005;6:31-36.
74. Smith SD, Bolwell BJ, Advani AS, et al. High rate of survival in transformed lymphoma after autologous stem cell transplant: pathologic analysis and comparison with *de novo* diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2009;50:1625-1631.
75. Escalon MP, Stefanovic A, Venkatraman A, et al. Autologous transplantation for relapsed non-Hodgkin lymphoma using intravenous busulfan and cyclophosphamide as conditioning regimen: A single center experience. *Bone Marrow Transplant*. 2009;44:89-96.

76. Mey U, Jha V, Strehl J, et al. High dose chemotherapy with autologous stem cell transplantation in diffuse large B-cell lymphoma. *GMS Ger Med Sci*. 2007;5. Doc02.
77. Waheed F, Kancherla R, Seiter K, et al. High dose chemotherapy with thiotepa, mitoxantrone and carboplatin (TMJ) followed by autologous stem cell support in 100 consecutive lymphoma patients in a single centre: analysis of efficacy, toxicity and prognostic factors. *Leuk Lymphoma*. 2004;45:2253-2259.
78. Doocey RT, Toze CL, Connors JM, et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. *Br J Haematol*. 2005;131:223-230.
79. Sirvent A, Dhedin N, Michallet M, et al. Low nonrelapse mortality and prolonged long-term survival after reduced-intensity allogeneic stem cell transplantation for relapsed or refractory diffuse large B cell lymphoma: report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire. *Biol Blood Marrow Transplant*. 2009;16:78-85.
80. Kusumi E, Kami M, Kanda Y, et al. Reduced-intensity hematopoietic stem-cell transplantation for malignant lymphoma: a retrospective survey of 112 adult patients in Japan. *Bone Marrow Transplant*. 2005;36:205-213.
81. Thomson KJ, Morris EC, Bloor A, et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin lymphoma. *J Clin Oncol*. 2009;27:426-432.
82. Rezvani A, Norasetthada L, Gooley T, et al. Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: a multicentre experience. *Br J Haematol*. 2008;143:395-403.

APPENDIX A: METHODOLOGY OF THE DIFFUSE LARGE B CELL LYMPHOMA EVIDENCE-BASED REVIEW UPDATE

Introduction

In 1999, the American Society for Blood and Marrow Transplantation (ASBMT) began developing systematic evidence-based reviews (EBR) and position statements on the effectiveness of autologous and allogeneic hematopoietic stem cell transplantation (SCT) for specific diseases. The purpose of these reviews is to provide evidence in support of clinical decisions and matters of public policy regarding SCT and achieve broader and more consistent coverage from payers for established indications for SCT. The ASBMT EBR Steering Committee developed specific policies outlining the methodology to be followed for these reviews [1,2]. Currently, eight 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 lymphoma (DLBCL) [3], multiple myeloma [4], pediatric acute lymphoblastic leukemia (ALL) [5], adult ALL [6], pediatric acute myelogenous leukemia (AML) [7], adult AML [8], myelodysplastic syndromes (MDS) [9], and follicular lymphoma [10].

In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly at approximately five-year intervals. The purpose of the updates is to provide a summary of recent clinical evidence, provide timely treatment recommendations, and determine if new evidence strengthens or changes the treatment recommendations provided in the original EBR. By providing these updates, physicians will have access to timely information that will facilitate and help disseminate advances in the field of transplantation. To guide its own activities and that of the expert panel associated with each review, the ASBMT EBR Steering Committee developed a policy statement specifying the methodology to be followed for updating each review [11]. The same expert panel members associated with the original EBR are invited to participate in the update process as well.

Expert Panel Selection for EBRs

To achieve an appropriate balance, physicians who have extensive clinical experience and published research studies using SCT and other therapies in the treatment of the specific disease of interest are invited to join an independent expert panel that examines the summarized literature and provides subsequent treatment recommendations based on the available evidence. 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.), which may result in different expert recommendations based on considerations of costs and access to care. In addition to clinical and research physicians, at least one third-party payer representative, a patient advocate, and a liaison to the ASBMT Steering Committee are invited to serve on the panel.

Literature Search Methodology for the DLBCL Update

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 first searched on June 10, 2008, using the search terms "diffuse large B cell lymphoma" OR "DLBCL" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2001, or later. Updated searches were conducted on April 10, 2009, and November 4, 2009. In addition to the online database searches, a manual search of the reference lists of the included articles and relevant reviews published since 2000 was conducted. Papers that were published before January 2001, included fewer than 25 DLBCL 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. Unlike the original DLBCL EBR, abstracts and presentations at national or international meetings were not used for the treatment recommendations in this update for reasons previously described [5]. However, abstracts are included in the "Areas of Needed Research and Ongoing Studies" section for the reader's information. Many of the studies evaluated for inclusion in this DLBCL update presented results for high risk or aggressive lymphoma; therefore, to be included, at least 60% of a study's patients had to have DLBCL, unless the results were stratified by histologic subtype of lymphoma.

Qualitative and Quantitative Grading of the Evidence

The hierarchy of evidence, including a new 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 [2]. Appendix A, and Tables 1 and 2, reprinted from the policy statement, define criteria used to grade the studies that were included in this update and criteria to grade the treatment recommendations, respectively. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment protocol also were considered in evaluating

Appendix A, 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-control or cohort studies. 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-control 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
(Reprinted with permission from Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J.* 2001;323:334-336.)

the studies. Clinical studies are described in the tables with sufficient detail to give a concise summary of study design and patient outcomes.

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.

Format of the DLBCL Update

Evidence is taken from studies published after 2000, which included DLBCL patients 15 years of age. Studies of "aggressive lymphoma" or "high-risk lymphoma" patients are included if DLBCL 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. As noted earlier, unlike the original DLBCL EBR, in which each article was summarized in detail in the text, this update presents the study design, patient population, and clinical outcomes only in the detailed summary tables. The highest quality studies are presented in the tables first, whereas studies of equal quality are presented in descending order by study population size. When specific data elements of a study's patient population or disease characteristics were not included in a table, it was because the information was not provided in the article.

Appendix A, 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+
(Reprinted with permission from Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J.* 2001;323:334-336.)

Consensus Process for Treatment Recommendations

The Treatment Recommendations Table (Table 1 in the DLBCL Update) contains the summary of consensus treatment recommendations made by the 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 Appendix A Table 2. The information is summarized by the primary authors in the Treatment Recommendations Table 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 and is then approved by the EBR Steering Committee and the ASBMT Executive Committee before submission to the journal. Any changes requested during the peer-review process must be reviewed and approved by all the expert panelists.

REFERENCES

1. Jones R, Horowitz M, Wall D, et al. ASBMT Policy Statement regarding the methodology of evidence-based reviews in evaluating the role of blood and marrow transplantation in the treatment of selected diseases. *Biol Blood Marrow Transplant*. 2000;6: 524-525.
2. Jones R, Nieto Y, Rizzo J, et al. The evolution of the evidence-based review: evaluating the science enhances the art of medicine-statement of the Steering Committee for Evidence-Based Reviews of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2005;11:819-822.
3. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2001;7: 308-331.
4. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant*. 2003;9:4-37.
5. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of

acute lymphoblastic leukemia in children: an evidencebased review. *Biol Blood Marrow Transplant*. 2005;11:823-861.
6. Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2006;12:1-30.
7. Oliansky DM, Rizzo JD, Aplan PD, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant*. 2007;13:1-25.
8. Oliansky DM, Appelbaum F, Cassileth PA, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute myeloid leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2008;14:137-180.
9. Oliansky DM, Antin J, Bennett J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. *Biol Blood and Marrow Transplant*. 2009;15:137-172.
10. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2010;16:443-468.
11. Jones RB, Nieto Y, Wall D, et al. Methodology for updating published evidence-based reviews evaluating the role of blood and marrow transplantation in the treatment of selected diseases: a policy statement by the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2009;15:761-762.

Appendix B. Comparative Studies of Autologous SCT Not Used for DLBCL TX Recommendations

Study Design						Patient Outcomes			
		Disease (at Dx unless stated) and Transplant Characteristics				Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group	Disease Characteristic	Treatment Groups	*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
UPDATE DATA (POST-2000 STUDIES)								
RITUXIMAB VERSUS NO RITUXIMAB PRIOR TO AUTOLOGOUS SCT FOR *DE NOVO* OR RELAPSED DLBCL								
[32]	**No Ritux**		**No Ritux**	**Ritux**	All	(2.6 y, .75-5.6 y)	**No Ritux**	**Ritux**	
Vellenga 2008		*Diagnoses*			>.05		(112)	(113)	
	Induction:	Relapsed or refractory							
1+	CHOP (83%)	aggressive NHL	100%	100%		(ITT)			
	Prior Ritux (4%)								
2000-2005		*Hist. Subtypes*				Completed			
HOVON Multicenter	*Salvage Tx:*	DLBCL	88%	91%		assigned Tx	46%	63%	
Enrolled n = 239	DHAP	Grade III Follicular	10%	6%					
Randomized n = 225		Other	2%	3%		Overall CR	35%	46%	**.003**
	VIM								
Med Age (range)		*B symptoms*	22%	25%		2-year PFS	31%	52%	**.002**
No Ritux 53 y (25-65)	*HDT:* BEAM								
Ritux 56 y (25-65)		*Risk Factors*				2-year OS	52%	59%	.15
	Auto SCT	aaIPI ≥3	75%	85%					
		LDH >Normal	50%	57%					
	± RT for bulky disease	WHO PS = 1	38%	35%					
[33]	**No Induction Ritux**		**No Induct. Ritux**	**Induction Ritux**		(2.4 y,.50-6.9 y)	**No Induct. Ritux**	**Induction Ritux**	
Martin 2008		*Diagnoses*					(69)	(94)	
2++	*Induction:*	Relapsed or refractory							
	CHOP-like, No Ritux	DLBCL	100%	100%		Completed			
2000-2007						HDT & SCT	65.2%	59.6%	>.10
GEL/TAMO Multicenter (25)	*Salvage Tx:*	*Prior auto SCT*	18.8%	3.2%	**.001**				
Retrospective	1-6× Ritux + ESHAP					Overall CR	56%	37%	**.015**
Analyzed n = 163		*Prior Chemo Reg ≥2*	29%	8.5%	**.001**				
	HDT: Mostly BEAM					TRM	1.4	2.1	>.10
Med Age (range)	Or BEAC	*R-ESHAP cycles ≥3*	72.5%	50%	**.004**				
No Ritux 53 y (19-70)						3-year PFS	57%	17%	**<.001**
Ritux 55 y (23-70)	Auto SCT	*Bulky disease*	24.6%	30.4%	>.10		CI 44%-70%	CI 13%-32%	
		B symptoms	15.8%	30.9%	**.044**	3-year OS	67%	38%	**<.001**
							CI 56%-79%	CI 25%-51%	
		Risk Factors							
		aaIPI ≥3	6.1%	7.7%	>.10				
		Stage ≥III	60.8%	62.7%	>.10				
		LDH >Normal	41%	44%	>.10				
		≥2 Ex-nodal sites	49.3%	47.9%	>.10				

(*Continued*)

Appendix B. (*Continued*)

Study Design							Patient Outcomes			
			Disease (at Dx unless stated) and Transplant Characteristics					Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease Characteristic	Treatment Groups		*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
[34]	**No Ritux**	**Ritux**		**No Ritux**	**Ritux**		**No Ritux**	**No Ritux**	**Ritux**	
Vitolo 2009	**(Historical Control)**		*Diagnoses*				(6 y)	(41)	(94)	
			de novo Aggressive	100%	100%		**Ritux**			
2++	8× MACOP-B	4× Ritux+MegaCEOP	B cell lymphomas				(4.1y)			
							(Ranges not stated)			
2002-2005	2× MAD	2× Ritux + MAD	*Hist. Subtypes*			.43				
GIMURELL Multicenter			DLBCL	85%	86%					
Prospective trial n = 94	± RT for bulky disease	± RT for bulky disease	PMBL	15%	11%		(ITT)			
1991-1995			Grade IIIb Follicular	0%	3%					
Historical Control n = 41	*HDT:* BEAM	*HDT:* BEAM					Completed			
Total analyzed n = 135			*BM Involvement*	44%	28%	.07	Assigned Tx	76%	81%	
	Auto PBSCT	Auto PBSCT								
Med Age (range)			*B symptoms*	59%	48%	.492	Overall CR	Not stated	82%	
No Ritux 46 y (19-59)										
Ritux 47 y (19-60)			*Bulky disease*	61%	45%	.094	4-year FFS	44%	73%	**.001**
								CI not stated	CI 63.5%-82.5%	
			Risk Factors							
			aaIPI ≥3	100%	100%	1.00				
			Stage ≥III	100%	100%	1.00	4-year OS	54%	80%	**.002**
			≥2 Ex-nodal sites	54%	35%	.056		CI not stated	CI 71.6%-88.4%	
			PS ≥2	63%	64%	1.00				
[35]	**No Ritux**	**Ritux**		**No Ritux**	**Ritux**		**No Ritux**	**No Ritux**	**Ritux**	
Fenske 2009			*Diagnoses*				(3.5 y, .08-9.7 y)	(818)	(176)	
		Ritux as first-line 38%	DLBCL	100%	100%					
2+		Ritux as salvage 62%					**Ritux**			
			Disease Status at SCT			.45	(3.5 y, .17-6.9 y)			
1996-2003	*HDT*	*HDT*	CR1	17%	22%					
CIBMTR Multicenter	TBI-based (14%)	TBI-based (15%)	CR2	16%	20%					
Retrospective	BEAM or like (64%)	BEAM or like (58%)	PIF-sensitive	20%	18%		3-year NRM	16%	11%	.06
Analyzed n = 994	CBV or like (9%)	CBV or like (15%)	PIF-resistant	6%	7%					
	Bu-Mel/Bu-Cy (6%)	Bu-Mel/Bu-Cy (6%)	Relapse-sensitive	34%	25%		3-year PFS	38%	50%	**.008**
Med Age (range)	Other (7%)	Other (6%)	Relapse-resistant	7%	8%					
No Ritux 52 y (18-75)							3-year OS	45%	57%	**.006**
Ritux 58 y (20-76)	Auto PBSCT (92%)	Auto PBSCT (94%)	*Prior Chemo Reg* >2	40%	57%	**< .001**				
(*P* < .001)	Auto BMT (8%)	Auto BMT (6%)								
			Med Dx to SCT	1.1 y	1.2 y	.46				
	± RT for bulky disease	± RT for bulky disease	(range)	(.25-17 y)	(.17-23 y)					
		No Ritux as part of conditioning or as post-SCT maintenance	*BM Involvement*	5%	2%	.06				
			Bulky disease	35%	27%	.23				
			Risk Factors							

(*Continued*)

Appendix B. (*Continued*)

Study Design							Patient Outcomes			
			Disease (at Dx unless stated) and Transplant Characteristics					Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease Characteristic	Treatment Groups		*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
			aaIPI ≥3 @ SCT	16%	11%	.27				
			Stage ≥III	65%	71%	.10				
			Karnofsky PS <90	37%	39%	.66				
[36]	**No Ritux (ICE)**	**Ritux (RICE)**		**No Ritux**	**Ritux**			**No Ritux**	**Ritux**	
Kewalramani 2004	**(Historical Control)**		*Diagnoses*				(2.4 y, Not stated)	(147)	(36)	
			Refractory or relapsed							
2−	3x ICE	3x RICE	DLBCL	100%	100%					
		(included 4x Ritux)					Completed assigned Tx	65%	78%	
Study years not stated	*HDT* not stated		*Risk Factors*							
Single Center		*HDT:* BEAM,	Age >60 y	12%	50%	.10				
Prospective trial n = 36	Auto SCT	TBI + Ifo + VP-16 ,	aaIPI ≥2	60%	47%	.19	CR post-ICE or RICE	27%	53%	**.01**
Historical control n = 147	(Details not stated)	TBI + Cy + VP-16, or CBV	Stage ≥III	79%	72%	.38		CI 20%-34%	CI 36%-69%	
			LDH >Normal	42%	50%	.45				
Med Age (range)			Karnofsky PS <80	34%	22%	.23				
No Ritux 48 y (18-68)		Auto PBSCT					Overall			
Ritux 45 y (23-72)		+ GF					Response rate	71%	78%	.53
							2-year PFS	43%	54%	.25
								CI 34%-55%	CI 38%-78%	
							2-year OS	56%	67%	.53
								CI 47%-67%	CI 50%-89%	
[37]	**No Ritux (LEED)**	**Ritux (R-LEED)**		**No Ritux**	**Ritux**	Not	**LEED**	**No Ritux**	**Ritux**	
Han 2006			*Diagnoses*			Stated	(2.4 y)	(26)	(24)	
	Induction/Salvage	*Induction/Salvage*	aggressive or relapsed				**R-LEED**			
2−	CHOP for *de novo*	CHOP for *de novo*	NHL	100%	100%		(1.5 y)			
	EPOCH, VADE, or	EPOCH, VADE, or					(Ranges not stated)			
2001-2005	DeVIC for salvage	DeVIC for salvage	*Hist. Subtypes*							
Single Center			DLBCL	50%	75%					
Prospective	*HDT*	*HDT*	T cell lymphoma	39%	9%		TRM	0%	0%	
n = 50	LEED	LEED + Ritux	MC	8%	0%					
	(pts >70 y rec'd	(pts >70 y rec'd	Lymphoblastic	3%	0%		PFS	79.6%	66.9%	Not stated
Med Age (range)	30% reduction of full	30% reduction of full	SLL	0%	4%					
No Ritux 63.5 y (28-78)	dosage)	dosage)	FL	0%	4%					
Ritux 60 y (42-74)			Burkitt	0%	4%		OS	78.2%	66.5%	Not stated
	Auto SCT + GF	Auto SCT +GF	Intravascular B cell	0%	4%					
			Disease Status at SCT							
			CR1	46%	67%					
			≥CR2	23%	16%					
			PR	27%	17%					
			Refractory	4%	0%					
			BM Involvement	23%	17%					
			Risk Factors							
			Age >70 y	19%	21%					
			aaIPI ≥3	81%	92%					
			Stage ≥III	92%	92%					

(*Continued*)

Appendix B. (*Continued*)

[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease (at Dx unless stated) and Transplant Characteristics: Disease Characteristic	Treatment Groups		P	Patient Outcomes: Follow-up (Med, Range) & Pt. Outcomes	Treatment Groups (n)	Treatment Groups (n)	P
RITUXIMAB VERSUS NO RITUXIMAB BEFORE AND AFTER AUTO SCT FOR RELAPSED AGGRESSIVE B-CELL NHL										
[38]	**No Ritux**	**Ritux**		**No Ritux**	Ritux	All	**No Ritux**	**No Ritux**	**Ritux**	
Khouri 2005			*Diagnoses*			> .05	(2.5 y, .17-8.3 y)	(30)	(67)	
2++	Unspecified chemo	1× Ritux 1 day prior to unspec. chemo + GF	*aggress.* B cell NHL	100%	100%					
							Ritux			
			Hist. Subtypes				(1.7 y, .17-3.5 y)			
2000-2003			DLBCL	57%	61%	.40				
Single Center	*PBSC Mobilization*	*PBSC Mobilization*	FL	43%	39%					
Prospective trial n = 67	Ifo + VP-16 + GF	Cy (n = 34) or					TRM	0%	0%	
1994-1996		Ifo + VP-16 (n = 33)	*Disease Status at SCT*							
Historical Control n = 30		+ GF + Ritux	PIF sensitive	0%	36%	**<.01**	2- year DFS	43%	67%	**.004**
Total analyzed n = 97			1st relapse, sensitive	80%	51%	**.01**		CI 26%-60%	CI 51%-79%	
	HDT	*HDT*	>1st relapse sensitive	17%	7%	.30				
Med Age (range)	BEAM	BEAM	Stable, untreated	3%	6%	.50	2-year OS	53%	80%	**.002**
No Ritux 51 y (27-60)								CI 34%-69%	CI 65%-89%	
Ritux 51 y (20-65)	Auto PBSCT + GF	Auto PBSCT + GF + Ritux 1 and 8 days after PBSCT	*Med # Chemo Reg* (range)	2 (2-4)	2 (1-5)	.20				
			Med Dx to SCT (range)	2.1 y (.67-10 y)	1.8 y (.33-12 y)	.60				
			BM Involvement	77%	84%	.40				
			Risk Factors							
			Age >60	0%	21%	**.007**				
			IPI ≥2 at SCT	0%	18%	**.01**				
			Stage ≥III	40%	24%	.10				
			LDH >Normal	13%	21%	.30				
[39]	**No Ritux**	**Ritux**		**No Ritux**	**Ritux**			**No Ritux**	**Ritux**	
Tarella 2008			*Diagnoses*				(5 y, Not stated)	(396)	(349)	
2+	*HDS*	*HDS*	HR B Cell NHL	100%	100%					
	Cy + GF	Cy + GF	*Hist. Subtypes*				Completed			
1986-2005	↓	↓	DLBCL	73%	67%		assigned Tx	90%	87%	
GITIL Multicenter (10)	MTX + VP-16 + GF	4x Ritux	FL	27%	33%					
Retrospective	↓	↓					Overall CR	73%	81%	
Analyzed n = 745	± Ara-C	MTX + VP-16 + GF	*HDS Use*							
DLBCL n = 522 (stratified)	↓	↓	First-line therapy	61%	49%		TRM	3.3%	2.8%	.91
	Auto PBSCT	± Ara-C	Salvage therapy:	39%	51%					
Med Age (range)		↓	PR	23%	9%		DLBCL Only:			
No Ritux 44 y (17-65)	± RT for bulky disease	Auto PBSCT	Ref/Relapsed	77%	91%	**.002**	5-year EFS	53%	58%	**.006**
Ritux 49 y (18-65)		↓								
		2× Ritux	*Salvage pts who rec'd*				5-year OS	57%	63%	**.005**
			Ritux in first-line Tx	1%	26%					
		± RT for bulky disease								

(*Continued*)

Appendix B. (*Continued*)

Study Design			Disease (at Dx unless stated) and Transplant Characteristics				Patient Outcomes			
								Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	Protocols by Treatment Group		Disease Characteristic	Treatment Groups		*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
			HDS Scheme Rec'd			**< .05**				
			Original	79%	11%					
			Ara-C supplemented	21%	89%					
			BM Involvement	28%	39%	**< .001**				
			Risk Factors							
			Age ≥47 y	42%	54%	**.009**				
			aaIPI ≥2	59%	63%	> .05				
[40]	**No Ritux**	**Ritux**		**No Ritux**	**Ritux**	Not	**No Ritux**	**No Ritux**	**Ritux**	
Kamezaki 2007			*Diagnoses*			Stated	(4.3 y)	(20)	(23)	
	Induction	*Induction*	*de novo* DLBCL	100%	100%		**Ritux**			
2−	6× CHOP	6x CHOP + 4× Ritux					(2.6 y)			
			Stage III or IV	100%	100%		(Ranges not stated)			
2001-2006	*PBSC Mobilization*	*PBSC Mobilization*								
Multicenter	VP-16 + GF	Ritux +	*Disease Status at SCT*			.37				
Retrospective		VP-16 + GF	CR	45%	57%		TRM	0%	0%	
n = 43			CRu	40%	30%					
	HDT	*HDT*	PR	15%	13%		1- year PFS	78.3%	80.2%	.59
Med Age (range)	Ranimustine +	Ranimustine +								
No Ritux 52 y (15-65)	Carboplatin +	Carboplatin +	*Med Dx to SCT*	.47 y	.48 y	.43				
Ritux 58 y (21-65)	VP-16	Ritux + VP-16	(range)	(.38-.82 y)	(.37-.71 y)					
	Auto PBSCT+ GF	Auto PBSCT + GF + Ritux on day -9 and + 1 after PBSCT (Total 8× Ritux)								
TIMING OF AUTOLOGOUS SCT										
								TILC <55 d	**TILC ≥55 d**	
[41] Holtan 2006	**TILC <55 d**	**TILC ≥55 d**		**TILC <55 d**	**TILC ≥55 d**		(2.9 y, .08 - 12.1 y)	(89)	(71)	
	BEAM (60%)	BEAM (52%)	*Diagnoses*							
2+	BEAC (37%)	BEAC (41%)	NHL	100%	100%		5-year PFS	31%	52%	**<.001**
	Cy+TBI (3%)	Cy+TBI (7%)								
1996-2001			*Hist. Subgroups*				5-year OS	39%	64%	**<.001**
Single Center	Auto BMT	Auto BMT	DLBCL	66%	63%	.10				
Retrospective analysis			FL	14%	21%					
n = 160			T cell	10%	1.5%					
			MC	7%	13%					
Med Age (range)			Other	3%	1.5%					
TILC < 55 d 52 y (23-73)										
TILC ≥ 55 d 54 y (31-72)			*Disease Status at SCT*			.50				
(*P* = .96)			CR	11%	17%					

(*Continued*)

Appendix B. (*Continued*)

Study Design						Patient Outcomes			
		Disease (at Dx unless stated) and Transplant Characteristics					Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	**Protocols by Treatment Group**	Disease Characteristic	Treatment Groups		*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
		PR	84%	79%					
		First relapse	1%	1.5%					
		Second relapse	2%	0%					
		Refractory	2%	2.5%					
		Prior Chemo Reg >2	25%	24%	.45				
		Risk Factors							
		Age ≥60	33%	30%	.73				
		IPI ≥3	14%	7%	.62				
		Stage ≥III	71%	63%	.40				
		LDH >Normal	34%	28%	.49				
		≥2 Ex-nodal sites	6%	3%	**.02**				
		PS ≥2	6%	4%	.18				
INTENSIVE VERSUS NON-INTENSIVE STEM CELL MOBILIZATION PRIOR TO AUTOLOGOUS PBSCT									
[42] Damon 2008	**Nonintense (SR for relapse)**	**Intense (HR for relapse)**		**Nonintense**	**Intense**		(2.5 y, .10-7.6 y)	**Nonintense** (30)	**Intense** (50)	
			Diagnoses							
2+	*Salvage*	*Salvage*	HR NHL	100%	100%					
	(R)CHOP or ESHAP	(R)CHOP or								
1999-2005	or Other or None	(R)ESHAP or	*PIF*	40%	56%	.34	TRM	0%	6%	
Single Center		(R)ICE or Other								
Retrospective analysis		or None	*CR1 <1 year*				DLBCL only:			
N = 80			(number/evaluable)	6/21	16/28	**.04**	4-year EFS	51 ± 29%	67 ± 22%	.96
	SC Mobilization	*SC Mobilization*								
Med Age (range)	Cy + GF	Cy + VP-16 ± Ritux	*In CR after salvage*	48%	35%	.23	4-year OS	56 ± 25%	76 ± 20%	**< .04**
Non-Intense 54 y (21-68)		or VP-16 + Ara-C								
Intense 55 y (23-69)		or VP-16 + Ara-C + Ritux	*Med # Chemo Reg* (range)	2 (1-6)	2 (1-5)	**.05**				
Hist. Subtypes										
DLBCL 54% (stratified)	*PBSC Purging*	*PBSC Purging*	*BM Involvement*	40%	44%	.87				
MC 15%	ex vivo with mAbs	ex vivo with mAbs								
LG transformed 12%	or in vivo with Ritux	or in vivo with Ritux	*Risk Factors*							
T-cell 7%	± GF	+ GF	IPI ≥3	29%	46%	.27				
Follicular (4%)			Stage ≥III	73%	88%	.21				
Primary CNS (4%)	*HDT:* CBV	*HDT:* CBV	LDH ≥Normal	40%	68%	**.01**				
Burkitt (2%)			>1 Ex-nodal sites	28%	36%	.44				
Intravascular (2%)	Auto PBSCT ± GF	Auto PBSCT ± GF	PS ≥2	7%	21%	.12				

(*Continued*)

Appendix B. (*Continued*)

Study Design						Patient Outcomes			
		Disease (at Dx unless stated) and Transplant Characteristics					Treatment Groups		
[Ref #], Quality & Strength of Evidence,* and Patient Population	**Protocols by Treatment Group**	Disease Characteristic	Treatment Groups	*P*	Follow-up (Med, Range) & Pt. Outcomes	(n)	(n)	*P*
COMPARISON OF ORAL VERSUS IV BUSULFAN PRIOR TO AUTOLOGOUS SCT								
[43]	**Oral Bu**		**Oral Bu**	**IV Bu**	Not stated	(8 y, 7-11 y)	**Oral Bu** (18)	**IV Bu** (31)	
Aggarwal 2006		*Diagnoses*							
2−	*PBSC Mobilization* GF	HR Aggressive NHL	100%	100%					
		Hist. Subtypes				TRM	28%	3%	**.01**
1994-2003	*HDT*	DLBCL	89%	77%					
Single Center	Oral Bu + Cy + VP-16	T cell	0%	10%		4-year PFS	17%	50%	**.008**
Retrospective		MC	5.5%	7%					
Total n = 49	Auto PBSCT	Burkitt	0%	3%		4-year OS	28%	58%	**.01**
		Anaplastic	0%	3%					
Med Age (range)		Immunoblastic	5.5%	0%					
Oral Bu 53 y (18-69)									
IV Bu 51 y (19-68)		*Disease Status at SCT*							
		PR1	0%	3%					
		≥CR2	22%	13%					
		PIF	17%	16%					
		Relapse—sensitive	39%	39%					
		Relapse—resistant	5%	16%					
		Relapse—untreated	17%	13%					
		# of Chemo Reg >2	94%	81%					
		Risk Factors							
		Age >60 y	17%	23%					
		aaIPI ≥3	34%	29%					
		Stage ≥III	100%	100%					
		LDH ≥Normal	33%	29%					
		Karnofsky PS <90	56%	29%					

aaIPI indicates age-adjusted International Prognostic Index; AC/ACE, doxorubicin/cyclophosphamide/etoposide/prednisone; ACVBP, doxorubicin/cyclophosphamide/vindesine/ bleomycin/prednisone; Ara-C, cytarabine; Auto; autologous; BEAC, carmustine/etoposide/cyclophosphamide/cytarabine; BEAM, carmustine/etoposide/cytarabine/melphalan; BM, bone marrow; Bu, busulfan; CBV, cyclophosphamide/carmustine/etoposide; CHOP, cyclophophamide/doxorubicin/vincristine/prednisone; CI, 95% confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; CRu, CR unconfirmed; Cy, cyclosphosphamide; DeVIC, carboplatin/ etoposide/ifosfamide/dexamethasone; DHAP, cisplatin/cytarabine/dexamethasone; DFS, disease-free survival; DLBCL, diffuse large B cell lymphoma; Dx, diagnosis; EFS, event-free survival; EPOCH, adriamycin/etoposide/vincristine/cyclophosphamide/prednisone; ESHAP, etoposide/cytarabine/methylprednisolone/cisplatin; FFS, failure-free survival; FL, follicular lymphoma; GEL/TAMO, Grupo Español de linfomas/Trasplante Autólogo de Médula Ósea; GF, growth factor; GIMURELL, Gruppo Italiano Multiregionale Linformi e Leucemie; GITIL, Gruppo Italiano Terapie Innnovative nei Linformi; HDS, high-dose sequential therapy; HDT, high-dose therapy; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; HR, high risk; ICE, ifosfamide/carboplatin/etoposide; Ifo, ifosphamide; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LEED, cyclophosphamide/etoposide/ melphalan/dexamethasone; MACOP-B, methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/ bleomycin; MAD, mitoxantrone/ cytarabine/dexamethasone; MC, mantle cell; MegaCEOP, cyclophosphamide/epirubicin/vincristine/prednisone; Mel, melphalan; Mito, mitoxantrone; MTX, methotrexate; NHL, non-Hodgkin Lymphoma; NRM, nonrelapse mortality; PBSCT, peripheral blood stem cell transplantation; PFS, progression-free survival; PIF, primary induction failure; PMBL, primary mediastinal B cell lymphoma; PR, partial remission; PS, performance status; OS, overall survival; RICE, ritux + ICE; Ritux, rituximab; RT, radiation therapy; SCT, stem cell transplantation; SLL, small lymphocytic lymphoma; TBI, total body irradiation; TRM, treatment-related mortality; Tx, treatment, VADE, vincristine/adriamycin/dexamethasone/etoposide; VIM, etoposide/ifosfamide/methotrexate; VP-16, etoposide, WF, working formulation.

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

Appendix C. Noncomparative Studies of Autologous SCT for DLBCL

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
UPDATE DATA (POST-2000 STUDIES)					
MULTIPLE OR TANDEM AUTOLOGOUS SCT AS FIRST-LINE THERAPY FOR DLBCL					
[44] Tarella 2007 2+ 1999-2004 GITIL Multicenter (6) Prospective n = 112 *Med Age (range)* 48 y (18-66)	*Debulking* 3× APO *HDS + Multiple Auto PBSCT* Cy + Ritux ↓ 6× Ara-C ↓ in vivo purged Auto PBSCT ↓ Ritux on days +8 and +18 ↓ VP-16 + Cisplatin ↓ in vivo purged Auto PBSCT ↓ Mito + Mel ↓ *in vivo* purged Auto PBSCT + Ritux on days +30 and +37 ± RT post-PBSCT for bulky dis.	*Diagnoses* *de novo* HR DLBCL *Hist. Subtypes* DLBCL PMBL Transformed T cell rich *aaIPI* 2 3 *Bulky disease* *BM Involvement* *Risk Factors* Stage ≥III LDH >normal ≥2 Ex-nodal sites PS ≥2	100% 79% 10% 8% 3% 66% 34% 52% 31% 81% 75% 30% 68%	[4 y (Not stated)] Completed Tx Overall CR (ITT) Early TRM 4-year EFS 4-year OS CI 68%-85%	 83% 80.4% 4.5% 73% CI 64%-81% 76%
[45] Glass 2006 2+ 1999-2004 Prospective Multicenter (31) Enrolled n = 124 Included n = 112 DLBCL n = 77 (73%) (Stratified) *Med Age (range)* 44 y (18-60)	4× MegaCHOEP (After courses 1 and 3 Cy + VP-16 doses escalated) *SC Mobilization* GF after courses 1 and 2 Auto PBSCT after courses 2, 3, and 4	*Diagnoses* *de novo* Aggress NHL *Hist. Subtypes* DLBCL T cell B cell unspecified FL MC Burkitt *Bulky Disease* *BM Involvement* *B Symptoms*	100% 73% 13% 7% 4% 2% 1% 64% 70% 65%	[4.6 y (Not stated)] Completed Tx Overall CR (ITT) Overall TRM <u>DLBCL Only</u> 5-year FFS 5-year OS	 81.8% 70% 4.5% 61.8% CI 50.4%-73.2% 62.6% CI 50.7%-74.5%

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Risk Factors			
		aaIPI ≥3	20%		
		Stage ≥III	61%		
		LDH >normal	100%		
		≥2 Ex-nodal sites	33%		
		PS ≥2	28%		
[46]	CEOP + GF (Cycles 1 & 2)	*Diagnoses*		[2.5 y (1.8-5.3 y)]	
Coso 2006		*de novo* HR NHL	100%		
	2x CEOP + VP-16 + Cisplatin + GF				
2+	(Cycles 3 & 4)	*Hist. Subtypes*		Completed Tx	83%
		DLBCL	94%		
1999-2002	Auto PBSCT after cycles 3 & 4	Anaplastic	6%	Overall CR	72%
Prospective R-ISC 98 Trial					
Enrolled n = 36	4× Ritux	*Risk Factors*		(ITT)	
Received Tandem Auto SCT n = 30		aaIPI ≥3	36%		
Received Ritux Post-Auto n = 24		Stage ≥III	89%	5-year EFS	63%
		LDH >normal	92%		CI 50%-81%
Med Age (range) 42 y (20-59)		≥2 Ex-nodal sites (n = 25)	28%		
		PS ≥2	42%	5-year OS	65%
					CI 52%-84%
				Rec'd Ritux (n = 24)	
					82%
				5-year EFS	CI 72%-100%
					86%
				5-year OS	CI 68%-99%
[47]	*Induction*	(Tandem Pts Only)		[3.5 y (Not stated)]	
Haioun 2001	4× ACVBP + GF				
		Diagnoses			
2+	*SC Mobilization*	*de novo* HR NHL	100%	(All 28 Pts)	
	Cy + VP-16 + GF				
1995-1997		*Hist. Subtypes*		Completed Tx	86%
Prospective Multicenter (4)	*1st Auto PBSCT*	DLBCL	73%		
Enrolled n = 36	*HDT:* BCV-Mito	T cell	27%	Overall CR	61%
Eligible for Auto SCT n = 28	followed by 1st reinfusion				
Tandem Auto SCT n = 24		*Bulky Disease*	75%	Overall TRM	11%
	2nd Auto PBSCT				
Med Age (range) 44 y (16-60)	*HDT:* BCM	*BM Involvement*	29%	Overall Relapse	32%
	Followed by 2nd reinfusion				
	(med 62 days after 1st)	*Risk Factors*			

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
				Tandem Only	
(This is the updated and published version of the Haioun et al. [48] abstract discussed in the original DLBCL EBR)	± GF	aaIPI ≥3	100%	(n = 24)	
		Stage ≥III	100%	3-year OS	
		LDH >normal	100%		67%
		≥2 Ex-nodal sites	71%		CI 43%-79%
		PS ≥2	54%		
MULTICENTER STUDIES OF AUTOLOGOUS SCT AS FIRST-LINE THERAPY FOR DLBCL					
[49]		*Diagnoses*		[6.5 y (.5-12.1 y)]	
Mounier 2004	*Induction*	*de novo* Aggress NHL	100%		
	4× ACVB				
2++		*Hist. Subtypes*		(All Pts)	
	HDT	DLBCL	55%		
1987-1993	BEAM or CBV	T cell	16%	Overall CR	61%
GELA LNH-87 and LNH-93 trials		Burkitt	15%	CRu	39%
Retrospective analysis	Auto SCT (61% BM)	Immunoblastic	3%		
Total n = 1734	± RT	FL	2%	TRM	1%
Subgroup analyzed n = 330		Unclassified	9%		
DLBCL n = 172 (55%) (Stratified)				Relapse	32%
		Bulky Disease	62%		
Med Age (range) 39 y (16-60)				5-year DFS	67 ± 5%
		Risk Factors			
		aaIPI ≥3	66%	5-year OS	75 ± 5%
		Stage ≥III	75%		
		LDH >normal	72%	DLBCL Only	
		≥2 Ex-nodal sites	43%	5-year DFS	68 ± 6%
		PS ≥2	23%		
				5-year OS	76 ± 5%
[50]	*Induction:* 4× MegaChop + GF	*Diagnoses*		[2.8 y (Not stated)]	
Arranz 2008		*de novo* Aggress NHL	100%		
	HDT: BEAM				
2++		*Hist. Subtypes*		Completed Tx	81%
	Auto SCT (94% PBSC)	DLBCL	86%		
2001-2005		PMBL	9%	Overall CR	85%
GEL/TAMO Multicenter		FL Grade 3	5%		
Prospective				(ITT)	
Enrolled n = 86		*Bulky Disease*	42%		
				TRM	7%
Med Age (range) 53 y (18-68)		*BM Involvement*	29%		
				5-year PFS	67%
		B Symptoms	58%		CI 55%-79%

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Risk Factors		5-year OS	74%
		IPI ≥3	79%		CI 59%-87%
		Stage ≥III	88%		
		LDH >normal	82%		
		PS ≥2	48%		
[51]	*Induction*	*Diagnoses*		[2.3 y (0-14 y)]	
Caballero 2003	CHOP (51%) or other	DLBCL	100%		
2+	*HDT*	*Status at SCT*		TRM	11%
	BEAM (39%) or BEAC (33%)	CR1 or PR1	53%		
1994-1999	or CBV (10%) or other chemo (5%)	>CR1 or PR1	35%	Relapse	11%
GEL/TAMO Multicenter	or Cy + TBI (12%)	Refractory	12%		
Retrospective analysis	± GF			5-year DFS	43%
Analyzed d n = 452		*Bulky Disease*	53%		
	Auto SCT (52% PBSC)			5-year OS	53%
Med Age (range) 42 y (15-73)		*BM Involvement*	22%		
Med Dx to SCT (range) .92 y (0.1-16.6 y)		*Prior Chemo Reg* ≥2	35%		
		Risk Factors			
		aaIPI ≥2	61%		
		Stage ≥III	73%		
		LDH >normal	62%		
		≥2 Ex-nodal sites	28%		
		PS ≥2	41%		
SINGLE CENTER STUDIES OF AUTO SCT AS FIRST-LINE THERAPY FOR DLBCL					
[52]	*HDS*	*Diagnoses*		[3.5 y (0.75-8.3 y)]	
Papajik 2008	PACEBO ± Ritux	*de novo* DLBCL	100%		
	↓				
2+	IVAM	*Status at SCT*		Overall CR	62%
	↓	CR	35%		
1999-2006	HAM	PR	65%	TRM	0%
Single Center					
Retrospective	*HDT:* BEAM	*Bulky Disease*	55%	Relapse	7%
n = 55					
	Auto PBSCT	*BM Involvement*	18%	5-year EFS	76%
Med Age (range) 41 y (19-62)	± RT				CI 63%-89%
		Risk Factors			
		Age ≥40 y	53%	5-year OS	85%
		IPI ≥3	36%		CI 73%-97%

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Stage ≥III	78%		
		≥2 Ex-nodal sites	58%		
		LDH >normal	60%		
[53]	*Induction*	*Diagnoses*		[4.1 y (1.2-6.1 y)]	
Stewart 2006	1× CHOP	*de novo* Aggress NHL	100%		
	↓				
2+	1x DICEP + GF	*Hist. Subtypes*		Completed Tx	93%
		DLBCL	94%		
1998-2004	*HDT:* BEAM	Burkitt	2%	NRM	2%
Single Center		FL Grade 3	2%		
Prospective	Auto PBSCT	T cell	2%	4-year EFS	72%
n = 55	± RT				CI 60%-84%
		Bulky Disease	62%		
Med Age (range) 44 y (20-63)				4-year OS	79%
		BM Involvement	29%		CI 69%-90%
		Risk Factors			
		aaIPI ≥3	35%		
		Stage ≥III	91%		
		LDH >normal	86%		
		≥2 Ex-nodal sites	66%		
		PS ≥2	78%		
[54]	*Induction*	*Diagnoses*		[2.9 y (1.3-9.3 y)]	
Vranovsky 2008	MACOP-B (10 weeks)	*de novo* Aggress NHL	100%		
2+	*Consolidation*	*Hist. Subtypes*		Completed Tx	93%
	2x DHAP or mini-BEAM	DLBCL	68%		
1997-2005		T cell	15%	100-day TRM	8.5%
Single Center	*HDT:* BEM or CBV	Anaplastic	11%		
Retrospective		MC	6%	5-year PFS	66%
n = 47	Auto PBSCT + GF				CI 49%-81%
		B Symptoms	81%		
Med Age (range) 44 y (20-60)				5-year OS	59%
		Bulky Disease	23%		CI 42%-76%
		BM Involvement	45%		
		Risk Factors			
		aaIPI ≥3	47%		
		Stage ≥III	98%		
		LDH > normal	89%		
		PS ≥2	45%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
[55]	*Induction*	*Diagnoses*		[10.2 y (7.2-12.3 y)]	
Bertz 2004	6× or 12× VACOP-B	*de novo* HG BCL	100%		
2+	*SC Mobilization*	*Hist. Subtypes*		Completed Tx	100%
	VP-16 + Ifo + Cisplatin + Epirubicin + GF	DLBCL	61%		
1992-1997		PMBL	21%	Overall CR	94%
Single Center		B Immunoblastic	12%		
Retrospective	*HDT*	Unclassified B cell	6%	TRM	0%
n = 33	BEAM or Bu + Cy				
		Bulky Disease	30%	10-y Relapse	16%
Med Age (range) 43 y (19-56)	Auto SCT + GF ± RT				
		Risk Factors		10-year DFS	76%
		AaIPI ≥3	67%		CI 67%-86%
		Stage ≥III	54%		
		LDH >normal	85%	10-year OS	79%
		≥2 Ex-nodal sites	27%		CI 68%-89%
		PS ≥2	52%		
PURGED AUTOLOGOUS SCT AFTER PRIMARY INDUCTION FAILURE					
[56]	*Induction*	*Diagnoses*		[7.3 y (0.1-16.3 y)]	
Benjamin 2009	CHOP (70%), R-CHOP (14%), or other (16%)	*de novo* DLBCL	100%		
2+		*Status at SCT*		Overall CR	77%
	PBSC Mobilization	PR	51%		
1988-2002	Cy or VP-16	SD	49%	NRM	12%
Single Center					
Retrospective	*HDT*	*Med Chemo Cycles (range)*	6 (2-12)	5-year EFS	59%
n = 43	Carmustine + VP-16 + Cy (60%)				CI 42%-74%
	or TBI + VP-16 + Cy (35%)	*Pre-SCT RT*	23%		
Med Age (range) 43 y (19-64)	or Lomustine + Cy + VP-16 (5%)			5-year OS	69%
		B Symptoms	60%		CI 55%-83%
Med Dx to SCT (range)	B-cell purged Auto SCT (86% PBSCT)			Secondary	
0.73 y (0.2 -1.3 y)	± RT	*Bulky Disease*	40%	MDS	5%
		BM Involvement	23%		
		Risk Factors			
		aaIPI ≥2	33%		
		Stage ≥III	72%		
		≥2 Ex-nodal sites	26%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
INTENSIFIED OR HIGH DOSE SEQUENTIAL THERAPY + AUTO SCT AS SALVAGE THERAPY FOR DLBCL					
[57]	*First-line Tx*	*Diagnoses*		[2 y (0.5-14.5 y)]	
Cortelazzo 2001	CHOP or MACOP-B/VACOP-B or Chlorambucil or Flu	Aggressive NHL	100%		
		Relapsed	63%		
2++		Refractory	37%	Overall CR	90%
	Debulking				
1985-1999	2× APO	*Hist. Subtypes*		TRM	4%
Retrospective Multicenter (9)		DLBCL	74%		
n = 103	*HDS*	T cell	26%	3-year EFS	44%
	HD Cy				CI 34%-54%
Med Age (range) 43 y (16-65)	↓	*Med Chemo Cycles (range)*	7 (3-17)		
	HD MTX + Vincristine			3-year OS	47%
	↓	*B Symptoms*	15%		CI 36%-59%
	HD VP-16			Secondary	
	+ GF	*Bulky Disease*	31%	Neoplasias	4%
	HDT	*BM Involvement*	20%		
	HD Mito + Mel or				
	BEAM or Thiotepa + L-PAM or	*Risk Factors*			
	HD Mel + TBI	IPI ≥2	37%		
		Stage ≥III	65%		
	Auto (89% PBSCT) ± GF	LDH >normal	27%		
	± RT	≥2 Ex-nodal sites	16%		
		PS ≥2	19%		
[58]	*SC Mobilization*	*Diagnoses*		[4 y (Not stated)]	
Robertson 2005	GF ± Cy	Aggressive NHL	100%		
	HDT	*Hist. Subtypes*		NRM	6%
2++	Augmented HD CBV	DLBCL	73%		
		Burkitt	7.5%	3-year PFS	36% ± 6%
1993-2001		Anaplastic	6%		
Prospective, Single Center	Unpurged Auto PBSCT	MC	4.5%	3-year OS	46% ± 8%
n = 67	+ GF	T Cell	4.5%		
		Other	4.5%	Secondary	
Med Age at SCT (range) 52 y (23-72)	No adjuvant Ritux			Neoplasias	0%
		Hist. Transformed	16%		
		Status at SCT			
		Refractory	42%		
		Early relapse	27%		
		Late relapse	28%		
		Other	3%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Prior Chemo Reg >2	18%		
		Bulky Disease	3%		
		LDH >normal	57%		
[59]	*Debulking*	*Diagnoses*		[2.1 y (0.1-6.3 y)]	
Josting 2005	2× DHAP + GF	Aggressive NHL	100%		
		Refractory	40%		
2+	*HDS*	Relapsed	60%	Overall CR	43%
	HD Cy + GF				
Study dates not stated	↓	*Hist. Subtypes*		TRM	0%
Prospective, Multicenter (13)	HD MTX + Vincristine	DLBCL	73%		
n = 57	↓	T Cell	19%	2-year FFS	25%
	HD VP-16 + GF	MC	2%		
Med Age at SCT (range) 43 y (24-65)		Other	6%	2-year OS	47%
	HDT: BEAM				
		Hist. Transformed DLBC	19%		
	Auto PBSCT + GF				
	± RT	*Prior RT*	28%		
		B Symptoms at Relapse	34%		
		Stage ≥III	54%		
AUTOLOGOUS SCT WITH RITUXIMAB AS SALVAGE THERAPY FOR DLBCL					
[60]	1× Ritux 1 day prior	*Diagnoses*		[5.5 y (1.4-12.2 y)]	
Alousi 2008	to unspecified chemomobilization	DLBCL	100%		
2+	Auto PBSCT	*Hist. Subtypes*		6-year TRM	6%
	+ Ritux on days 1 and 8 after PBSCT	DLBCL	78%		CI 3%-11%
1995-2005		DLBCL-transformed FL	22%		
Retrospective, Single Center				5-year PFS	48%
n = 174		*Status at SCT*			CI 40%-56%
		CR	12%		
Med Age (range) 47 y (16-75)		CRu	38%	5-year OS	62%
		PR	50%		CI 54%-69%
		Prior Chemo Reg >2	30%		
		Ritux pre/post PBSCT	37%		
		Risk Factors			
		Age ≥60	51%		
		IPI ≥1	30%		
		LDH >Normal	21%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
[61]	*SC Mobilization*	*Diagnoses*		[2.5 y (Not stated)]	
Horwitz 2004	Cy + GF	Aggressive NHL	100%		
				(ITT)	
2+	*HDT*	*Hist. Subtypes*			
	Carmustine + VP-16 + Cy	DLBCL	71%	NRM	3%
1998-2000	or TBI + VP-16 + Cy (8.5%)	Other B cell	11%		
Prospective, Single Center		Transformed	9%	2-year EFS	83%
n = 35	Purged (mAbs) Auto PBSCT ± GF	MC	9%		CI 70-95%
	↓				
Med Age at SCT (range) 51 y (28-70)	Day 42 Ritux weekly x 4	*Status at SCT*		2-year OS	88%
	↓	CR1	20%		CI 78%-99%
	Day 180 Ritux weekly x 4	Refractory	29%		
		Relapsed	51%	DLBCL Only	
				2-year EFS	81%
		Med Chemo Reg (range)	2 (Not stated)		CI 64%-98%
				2-year OS	85%
					CI 70%-100%
INVOLVED-FIELD RADIATION PRIOR TO HDT + AUTOLOGOUS SCT AS THERAPY FOR DLBCL					
[62]	*First-Line Therapy*	*Diagnoses*		[5 y (1.7-15.6 y)]	
Hoppe 2008	CHOP (81%) or Dox-based (18%) or Unknown (1%)	DLBCL	100%		
2+	± RT (10%)	*Hist. Subtypes*		TRM	6%
		DLBCL	87%		
1990-2006	Pretransplant IFRT	PMBL	13%	Relapsed	41%
Retrospective, Single Center	30 Gy (54%) or				
n = 164	18 Gy IFRT + 12 Gy TBI (as part of HDT regimen) (46%)	*Status at SCT*		5-year PFS	53%
		Refractory	24%		
Med Age (range) 46 y (17-73)		Relapsed	59%	5-year OS	58%
	HDT	Transformed (DLBCL			
	BEAM (42%)	at relapse)	8.5%	Secondary	
	Ifo + VP-16 (22.5%)	High risk (Stage IV bulky		Neoplasias	7%
	Cy + VP-16 (22.5%)	or high IPI score)	8.5%	MDS	2%
	CBV (7%)				
	Other (6%)	*Med IFRT dose (range)*	30 Gy (21-45)		
	(± 12 Gy TBI)				
		Med IFRT to SCT (range)	21 days (12-98)		
	Auto (85% PBSCT)				
		Bulky Disease	12%		
		BM Involvement	7%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Risk Factors			
		aaIPI ≥2	30%		
		Stage ≥III	49%		
		LDH > normal	49%		
		Ex-nodal sites involved	61%		
		PS ≥2	13%		
MULTICENTER STUDIES OF AUTOLOGOUS SCT AS SALVAGE THERAPY FOR DLBCL					
[63]	*HDT*	*Diagnoses*		[3.7 y (0.1-10.3 y)]	
Vose 2004	Chemotherapy only (32%)	Aggress. Diffuse NHL	100%		
	TBI-based regimen (68%)				
2++		*Hist. Subtypes*		TRM	6%
	Auto BMT (49%)	DLBCL	60%		
1989-1996	Auto PBSCT (41%)	Diffuse mixed cell	20%	3-yr Rel/Prog	63%
ABMTR Multicenter (93)	Auto with both BM and PBSC (10%)	Immunoblastic	20%		CI 58%-68%
Retrospective	± GF				
n = 429		*Status at SCT*		3-year PFS	31%
		CR2	35%		CI 27%-36%
Med Age at SCT (range) 49 y (5-71)		Relapse 1	65%		
				3-year OS	44%
		B Symptoms	35%		CI 33%-55%
		BM Involvement	14%		
		Risk Factors			
		Age ≥40 y	72%		
		Stage ≥III	62%		
		LDH >normal	31%		
		Ex-nodal sites involved	17%		
		Karnofsky PS <90%	34%		
[64]	*HDT*	*Diagnoses*		[3.4 y (2-8.6 y)]	
Vose 2001	TBI + Other (27%)	Aggress. Diffuse NHL	100%		
	BEAC (27%)				
2+	CBV (19%)	*Hist. Subtypes*		Overall CR	44%
	Other (27%)	DLBCL	60%		
1985-1995		Diffuse mixed cell	15%	100-Day NRM	39%
ABMTR Multicenter (48)	Auto BMT (56%)	Immunoblastic	25%		
Retrospective	Auto PBSCT (37%)			5-year PFS	31%
n = 184	Auto with both BM + PBSC (7%)	*Status at SCT*			CI 24%-38%
	± GF	Sensitive	60%		
Med Age at SCT (range) 42 y (9-69)	± RT	Resistant	28%	5-year OS	37%

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Unknown	12%	CI 30%-45%	
		B Symptoms	54%		
		BM Involvement	21%		
		Prior Chemo Reg ≥2	36%		
		Risk Factors			
		Stage ≥III	63%		
		LDH >normal	67%		
		Karnofsky PS <80%	14%		
[65]	*First-line Tx*	*Diagnoses*		[2.4 y (0.1-6.7 y)]	
Rodriguez 2004	CHOP (59%)	DLBCL	100%		
	Other (41%)				
2+		*Status at SCT*		Overall CR	54%
	HDT	PR	65%		
1990-1999	BEAM (44%)	Treatment failure	35%	TRM	8%
GEL/TAMO Multicenter	BEAC (28%)				
Retrospective	Cy + TBI (12%)	*B Symptoms*	53%	5-year DFS	63%
n = 114	CBV (10%)			(for CR pts)	
	Other (6%)	*BM Involvement*	19%		
Med Age at SCT (range) 40 y (13-73)				5-year OS	43%
	Auto BMT (30%)	*Bulky Disease*	69%		
	Auto PBSCT (63%)				
	Auto with both BM + PBSC (7%) ± GF	*Prior Chemo Reg* ≥2	56%		
		Risk Factors			
		aaIPI ≥2	73%		
		Stage ≥III	75%		
		LDH >normal	72%		
		Ex-nodal sites ≥2	31%		
		PS ≥2	53%		
SINGLE-CENTER STUDIES OF AUTOLOGOUS SCT AS SALVAGE THERAPY FOR DLBCL					
[66]	*First-line Tx*	*Diagnoses*		[5 y (1-14.2 y)]	
Lerner 2007	CHOP (61%)	DLBCL	100%		
	Other anthracycline-based regimen (34%)				
2++	Other (4%)	*Hist. Subtypes*		Overall CR	91%
		DLBCL	66%		
1984-2002	*HDT*	Diffuse mixed cell	14%	Pre 1993 TRM	19%
Retrospective, Single Center	TBI-based regimen (74%)	Immunoblastic	16%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
Analyzed n = 80	Chemotherapy only (26%)	Anaplastic	4%	Post 1993 TRM	2%
Med Age at SCT (range) 47 y (19-68)	Auto BMT (51%)	*Response to Salvage*		5-year PFS	32%
	Auto PBSCT (45%)	CR	34%		CI 22-42%
	Auto with both BM + PBSC (4%) ± GF	PR	66%		
				5-year OS	38%
		B Symptoms	25%		CI 27-50%
		BM Involvement	10%		
		Risk Factors			
		Age > 60 y	15%		
		IPI ≥2	13%		
		Stage ≥III	48%		
		LDH >normal	72%		
		Ex-nodal sites ≥2	20%		
		PS ≥2	20%		
[67]	DLBCL Pts. Only	*Diagnoses*		[Minimum 10 months (Not stated)]	
Sohn 2009		DLBCL	100%		
	HDT			DLBCL Only	
2++	BEAM (41%)	*Hist. Subtypes*			
	BEAC (41%)	DLBCL	70%	Overall CR	61%
1993-2006	Bu + Cy + VP-16 ± Yttrium-90 (18%)	T Cell	30%		
Retrospective, Single Center				2-year EFS	40%
n = 77	Auto SCT	DLBCL Pts. Only			CI 27%-53%
DLBCL n=54 (70%) (Stratified)					
		Status at SCT		2-year OS	46%
DLBCL Pts. Only		CR1	15%		CI 33%-59%
Med Age at SCT (range) 48 y (15-68)		PR1	24%		
		CR2	15%		
		PR2	29%		
		Refractory	17%		
		Timing of SCT			
		Front-line therapy	30%		
		First relapse	70%		
		Risk Factors			
		Age >60 y	15%		
		aaIPI ≥2	24%		
		IPI ≥3	17%		
		Stage ≥III	33%		
		LDH >normal	57%		
		Ex-nodal sites ≥2	13%		
		PS ≥2	6%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
[68]	*Second-line Tx*	*Diagnoses*		[4 y (0.67-8.2 y)]	
Hamlin 2003	ICE ± RT	DLBCL	100%		
2+	*HDT*	*Status at SCT*		Completed Tx	68%
	Chemotherapy only (57%)	Relapsed	55%		
1993-2000	TBI-based regimen (43%)	Refractory	45%	(ITT)	
Retrospective, Single Center					
n = 150	Auto SCT	*BM Involvement*	22%	4-year PFS	28%
Med Age at SCT (range) 49 y (16-68)		*Risk Factors*		4-year OS	34%
		Age ≥60 y	17%		
		aaIPI ≥2	60%		
		Stage ≥III	78%		
		LDH <normal	58%		
		Ex-nodal sites ≥2	44%		
		Karnofsky PS <80%	44%		
[69]	DLBCL Pts. Only	*Diagnoses*		[1.8 y (0.1-7.8 y)]	
Kuruvilla 2008		Rel/Ref B-cell NHL	100%		
	Initial Chemotherapy				
2+	CHOP or CHOP-like (89%)	*Hist. Subtypes*		DLBCL Only	
	Ritux + CHOP (10%)	DLBCL	79%		
1995-2004	ABVD (1%)	PMBL	21%	Completed Tx	50%
Retrospective, Single Center					
n = 180	*Salvage Tx*	DLBCL Pts. Only		TRM	1%
DLBCL n = 143 (79%) (Stratified)	DHAP, ESHAP, GDP, or mini-BEAM				
	+ GF	*Response to Salvage*		2-year PFS	36%
DLBCL Pts. Only		CR or CRu	12%		
Med Age at SCT (range) 53 y (21-66)	*2nd Line of Salvage Tx* (34%)	PR	36%	2-year OS	53%
		SD	17%		
	HDT	PD	35%		
	VP-16 + Mel + GF				
		Prior Radiation	23%		
	Auto BMT				
	± RT	*B Symptoms*	13%		
		Bulky Disease	21%		
		Risk Factors			
		Age >60 y	15%		
		IPI ≥2	42%		
		Stage ≥III	49%		
		LDH >normal	59%		
		Ex-nodal sites ≥2	9%		
		PS ≥2	19%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
[70]	*Salvage Tx*	*Diagnoses*		[2.8 y (0.1-13.7 y)]	
Song 2003	Cisplatin-based regimen or mini-BEAM	Rel/Ref NHL	100%		
2+	*HDT*	*Hist. Subtypes*		DLBCL Only	
	VP-16 + Mel ± TBI	DLBCL	73%		
1987-2001		T Cell	27%	Completed Tx	50%
Retrospective, Single Center	SC Source for DLBCL Pts. Only				
n = 133	Auto BMT (45%)	DLBCL Pts. Only		TRM	7%
DLBCL n = 97 (73%) (Stratified)	Auto PBSCT (41%)				
	Auto with both BM + PBSC (14%)	*Response to Salvage*		Relapsed	46%
DLBCL Pts. Only		CR	37%		
Med Age at SCT (range) 46 y (19-65)		PR	57%	3-year EFS	42%
		<PR	6%		CI 32%-53%
		Risk Factors		3-year OS	53%
		Stage ≥III	42%		CI 42%-64%
		LDH >normal	12%		
		Ex-nodal disease	25%		
[71]		*Diagnoses*		[6.3 y (Not stated)]	
Kewalramani 2006	*DLBCL HDT*	Rel/Ref NHL	100%		
	TBI-based regimen (56%)				
2+	Chemotherapy only (44%)	*Hist. Subtypes*		DLBCL Only	
		DLBCL	78%		
1993-2003	Auto SCT	T Cell	22%	5-year PFS	34%
Retrospective, Single Center					
n = 110		DLBCL Pts. Only		5-year OS	39%
DLBCL n = 86 (78%) (Stratified)					
		Response to Induction			
DLBCL Pts. Only		Refractory	30%		
Med Age at SCT (range) 47 y (18-68)		Relapse	70%		
		Response to Salvage			
		CR	41%		
		PR	59%		
		Risk Factors			
		aaIPI ≥3	54%		
		IPI ≥3	34%		
[72]	*PBSC Mobilization*	*Diagnoses*		[2.8 y (0.3-13.6 y)]	
McCoy 2004	Cy + GF	Relapsed NHL	100%		
2+	*HDT*	*Hist. Subtypes*		Day-100 CR Rate	62%
	Thiotepa + VP-16	DLBCL	76%		
1987-2001		FL	9%	NRM	8%
Retrospective, Single Center	Auto SCT (BM or PBSC or both)	Other Diffuse	7%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
n = 65		Anaplastic	5%	3-year EFS	32%
		T Cell	3%		CI 20%-45%
Med Age at SCT (range) 49 y (19-64)					
		Status at SCT		3-year OS	40%
		CR1	5%		CI 26%-53%
		CR2	26%		
		PR (includes 12 PIF)	46%		
		<PR (includes 8 PIF)	23%		
		Med Chemo Reg (range)	2 (1-6)		
		Stage ≥III	65%		
[73]	CHOP or BEAC for induction	*Diagnoses*		[2.8 y (.3-13.6 y)]	
Usui 2005	EPOCH for salvage	Aggressive NHL	100%		
2+	*HDT*	*Hist. Subtypes*		Day-100 CR Rate	62%
	ACNU	DLBCL	61%		
1991-2001		FL	12%	NRM	8%
Prospective, Single Center	Auto PBSCT (61%)	Other Diffuse	17%		
n = 56	Auto BMT (5%)	Immunoblastic	4%	3-year EFS	32%
	Auto with both BM + PBSC (34%)	Lymphoblastic	4%		CI 20%-45%
Med Age at SCT (range) 46 y (20-61)	± RT	Burkitt	2%		
				3-year OS	40%
		Status at SCT			CI 26%-53%
		CR1	16%		
		≥CR2	18%		
		PR1	25%		
		≥PR2	21%		
		No response	20%		
		Med PS (range)	1 (0-2)		
[74]	*PBSC Mobilization*	*Diagnoses*		[2.2 y (0.3-5 y)]	
Smith 2009	VP-16 ± GF	DLBCL	100%		
2+	*HDT*	*Hist. Subtypes*		*de novo* DLBCL	
	Bu + VP-16 + Cy	*de novo* DLBCL	55%		
2003-2008		HT DLBCL (from FL)	45%	3-year RFS	59%
Retrospective, Single Center	Auto PBSCT + GF				
n = 56		*SCT as Front-line Tx*	30%	3-year OS	59%
Med Age at SCT (range) 57 y (30-72)		*Prior Chemo Reg ≥3*	34%	HT DLBCL	
		Prior mAbs Tx	93%	3-year RFS	64%
		Refractory at SCT	9%	3-year OS	63%

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		Bulky Disease	18%		
		Risk Factors			
		IPI ≥3	20%		
		LDH >Normal	63%		
		Karnofsky PS <80%	27%		
[75]	*Salvage Tx:* Not specified	*Diagnoses*		[2.8 y (0.3 – 13.6 y)]	
Escalon 2009		Relapsed NHL	100%		
	PBSC Mobilization: GF				
2+		*Hist. Subtypes*		Day-100 NRM	9%
	HDT	DLBCL	65%		
2000-2005	Bu + Cy	FL	19%	DLBCL Only	
Retrospective, Single Center		MC	9%		
n = 43	Auto PBSCT	T Cell	7%	3-year EFS	35%
DLBCL n = 28 (65%) (Stratified)	+ GF				CI 18%-53%
		Prior Chemo Reg >2	40%		
Med Age at SCT (range) 50 y (20-68)				3-year PFS	41%
		Status at SCT			CI 21%-59%
		CR	58.5%		
		CRu	2.5%	3-year OS	34%
		PR	30%		CI 17%-53%
		SD	9%		
		Risk Factors			
		Age >60	21%		
		Stage ≥3	69%		
[76]	*HDT*	*Diagnoses*		[3.5 y (0.8-9.2 y)]	
Mey 2007	Mega-CHOEP or BEAM or CEI or CEIAP or IC	DLBCL	100%		
2+		*Status at SCT*		TRM	12%
	Auto PBSCT ± GF	CR	8%		
1996-2004		PR	60%	3-year OS	48%
Retrospective, Single Center		SD	16%		
n = 25		PD	16%		
Med Age at SCT (range) 43 y (18-69)		*BM Involvement*	12%		
		Bulky Disesase	40%		
		Prior Chemo Reg ≥2	48%		
		Risk Factors			
		Age >50 y	40%		
		IPI ≥3	52%		
		Stage ≥III	56%		

(*Continued*)

Appendix C. (*Continued*)

Study Design				Patient Outcomes	
(Ref #), Qual. & Strength of Evidence,* and Patient Population	Protocol	Disease and Transplant Characteristics		Follow-Up [Med (range)] & Patient Outcomes	
		LDH >normal	92%		
		Ex-nodal sites ≥2	60%		
		PS ≥2	4%		
[77]	*PBSC Mobilization*	*Diagnoses*		[7.6 y (1.9-12.3 y)]	
Waheed 2004	GF ± Cy + VP-16	NHL	63%		
		Hodgkin Disease	37%		
2−	*HDT*			Overall TRM	4%
	Thiotepa + Mito + Carboplatin	*NHL Hist. Subtypes*			
1990-2001		DLBCL	86%	Overall 5-y PFS	43%
Retrospective, Single Center	Auto BMT (18%)	T Cell	5%		
n = 100	Auto PBSCT (50%	FL Grade 3	3%	NHL Only	
NHL n = 63 (63%) (Stratified)	Auto with both BM + PBSC (32%)	MC	3%		
DLBCL (86% of NHL)		Lymphoblastic	1.5%	Median OS	8.9 years
		Anaplastic	1.5%		
Med Age at SCT (range) 44 y (21-72)					
		Med Serum LDH (range)	181 (86-667)		
		B Symptoms	29%		
		Prior RT	42%		
		Prior Chemo Reg ≥2	90%		
		Risk Factors			
		Stage ≥III	69%		
		PS ≥1	45%		

aaIPI indicates age-adjusted International Prognostic Index; ABMTR, Autologous Blood and Marrow Transplant Registry; ACNU, nimustine/etoposide/carboplatin/cyclophosphamide; ACVB, doxorubicin/mitoxantrone/cyclophosphamide; ACVPB, doxorubicin/cyclophosphamide/vindesine/bleomycin/methylprednisolone; APO, doxorubicin/vincristine/prednisone; Ara-C, cytarabine; Auto, autologous; BCL, B cell lymphoma; BCM, busulfan/carboplatin/melphalan; BCV-Mito, carmustine/cyclophosphamide/etoposide/mitoxantrone; BEAC, bleomycin/etoposide/doxorubicin/cyclophosphamide; BEAM, carmustine/etoposide/cytarabine/melphalan; BEM, carmustine/etoposide/melphalan; BM(T), bone marrow (transplantation); Bu, busulfan; CBV, cyclophosphamide/carmustine/etoposide; CEI, carboplatin/etoposide/ifosfamide; CEIAP, carboplatin/etoposide/ifosfamide/adriamycin/dexamethasone; CEOP, cyclophosphamide/epirubicin/vincristine/prednisone; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, 95% confidence interval; CR, complete remission; CRu, unconfirmed complete remission; Cy, cyclosphosphamide; DHAP, dexamethasone/cytarabine/cisplatin; DICEP, dose-intensive cyclophosphamide/etoposide/cisplatin; DLBCL, diffuse large B cell lymphoma; Dx, diagnosis; EFS, event-free survival; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; ESHAP, etoposide/cisplatin/methylprednisolone/cytarabine; FFS, failure-free survival; FL, follicular lymphoma; Flu, fludarabine; GDP, gemcitabine/dexamethasone/cisplatin; GEL/TAMO, Spanish Group for Lymphoma and Autologous Transplantation; GF, growth factor; GITIL, Gruppo Italiano Terapie Innovative nei Linfomi; HAM, cytarabine/mitoxantrone; HDS, high-dose sequential therapy; HDT, high-dose therapy; HG, high grade; HLA, human leukocyte antigen; HR, high risk; IC, thiotepa/busulfan/cyclophosphamide; Ifo, ifosphamide; IFRT, involved-field radiotherapy; IPI, International Prognostic Index; IVAM, ifosfamide/etoposide/cytarabine/methotrexate; LDH, lactate dehydrogenase; MACOP-B, methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin; MC, mantle cell; MegaCHOEP, cyclophosphamide/adriamycin/vincristine/etoposide/prednisone; Mel, melphalan; Mito, mitoxanthrone; NRM, nonrelapse mortality; PACEBO, prednisone/doxorubicin/cyclophosphamide/etoposide/bleomycin/vincristine; PBSC(T), peripheral blood stem cell (transplantation); PFS, progression-free survival; PMBL, primary mediastinal large B cell lymphoma; PR, partial remission; PS, performance status; ritux, Rituximab; OS, overall survival; R-ISC, ritux + intensive sequential chemotherapy; RT, radiation therapy; SCT, stem cell transplantation; SD, stable disease; SFGM-TC, Société Française de Greffe de Moelle et de Thérapie Cellulaire; TBI, total-body irradiation; TRM, treatment-related mortality; Tx, treatment, VACOP-B, doxorubicin/cyclophosphamide/vincristine/bleomycin; VP-16, etoposide.

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

Appendix D. Noncomparative Studies of Allogeneic SCT for DLBCL

Study Design					Patient Outcomes	
[Ref #], Qual. & Strength of Evidence,* and Patient Population	Protocol		Disease and Transplant Characteristics		Follow-Up [Med (Range)] & Patient Outcomes	
UPDATE DATA (POST-2000 STUDIES)						
MYELOABLATIVE ALLOGENEIC SCT FOR DLBCL						
[78]	*Prior Auto SCT*	0%	*Diagnoses*		[5 y (1.1-11.4 y)]	
Doocey 2005			Rel/Ref Aggressive NHL	100%		
	Conditioning					
2++	Cy + TBI	82%	*Hist. Subtypes*		1-year TRM	25%
	Cy + TBI + VP-16	14%	DLBCL	52%		CI 13%-39%
1987-2003	Bu + Cy	4%	Transformed B cell	37%		
Single Center			T cell lymphoma	11%	5-year EFS	43%
Retrospective	*Donors*					CI 27%-58%
n = 44	MRD	75%	*Response to Initial Chemo*			
	MUD	21%	CR	62%	5-year OS	48%
Med Age (range) 40 y (15-56)	MMUD	4%	PR	20%		CI 32%-63%
			Stable/Progressive Disease	18%		
Med Chemo Regimens (range) 2 (1-3)	BM (89%) or PB				5-year Relapse	32%
	Allo SCT		*Disease Status at SCT*			CI 18%-47%
Med Relapse to SCT (range) 0.33 y (0.1-1.1)			PR1	20%		
			Relapse—sensitive	60%		
			Relapse—resistant	11%		
			PIF	9%		
			BM Involvement	32%		
			Risk Factors			
			Transformed from FL	37%		
			Stage ≥III	80%		
REDUCED INTENSITY CONDITIONING ALLOGENEIC SCT FOR DLBCL						
[79]	*Prior Auto SCT*	79%	*Diagnoses*		[4.1 y (0.8-8 y)]	
Sirvent 2009			Ref/Rel DLBCL	100%		
	Conditioning					
2++	Flu-based chemo	74%	*Disease Status at SCT*		1-year NRM	23%
	Flu + 2 Gy TBI	25%	CR	47%		CI 12%-34%
1998-2007	Cy + 6 Gy TBI	1%	PR	34%		
SFGM-TC Multictr (23)	(No Ritux)		Stable or PD	17%	2-year PFS	44%
Retrospective						CI 32%-56%
n = 68	*Donors*		*>2 Prior Chemo Reg*	37%		
	MRD	84%			2-year OS	49%
Med Age (range) 48 y (17-66)	MUD	8%	*Risk Factors*			CI 37% -61%
	MMUD	2%	Transformed from FL	21%		
Med Dx to SCT (range) 1.8 y (0.4- 10.4 y)			IPI ≥2	47%	2-year Relapse	41%
	T cell depletion (ATG or mAbs) PB (82%), BM, or cord Allo SCT	56%				CI 28 - 54%

(*Continued*)

Appendix D. (*Continued*)

Study Design					Patient Outcomes	
[Ref #], Qual. & Strength of Evidence,* and Patient Population	Protocol		Disease and Transplant Characteristics		Follow-Up [Med (Range)] & Patient Outcomes	
[80]	Aggress/Highly Aggress Only		*Diagnoses*		[2 y (.3 – 3.7 y)]	
Kusumi 2005			Indolent NHL	40%		
	Prior Auto SCT	45%	Aggressive NHL	52%		
2+			Highly Aggressive NHL	8%	Overall	
	Prior RT	37%			3-year TRM	25.2%
1999-2002			Aggessive/Highly Aggress			
Multictr (32)	*Conditioning*		*Chemosensitivity at SCT*		Aggress. Only	
Retrospective	Flu-based chemo	79%	Sensitive	57%	3-year OS	48%
Total n = 112	Flu + 2 Gy TBI	4%	Resistant	43%		CI 35%-61%
Aggressive/Highly Aggress. n = 67 (60%)	2 Gy TBI	8%				
DLBCL n = 31 (28% of total; 46% A/HA)	Other	9%	*Risk Factors*		DLBCL Only	
(OS Stratified)			Transformed from FL	6%	3-year OS	31%
	Donors		LDH > normal	51%		CI 13%-49%
Aggressive/Highly Aggressive Only	MRD (sibling)	81%	PS ≥2	21%		
Med Age (range) 50 y (22-72)	MMRD	8%				
	MUD	11%				
Med Dx to SCT (range) 1.6 y (0.3-12.1 y)						
	T cell depletion	0%				
Med Chemo Regimens (range) 4 (1-14)						
	PB (80%) , BM, or cord Allo SCT					
[81]	*Prior Auto SCT*	71%	*Diagnoses*		[4.3 y (1.5–7.4 y)]	
Thomson 2009			de novo DLBCL	62%		
	Prior Ritux	56%	DLBCL, transformed FL	38%		
2+					4year NRM	32%
	Conditioning		*Chemosensitivity at SCT*			
1998-2006	Flu + Mel +		Sensitive	83%	4-year PFS	48%
Multictr (8)	Alemtuzumab	100%	Resistant	17%		
Retrospective					4-year OS	47%
n = 48	*Donors*					
	MRD	60%			4-year Relapse	33%
Med Age (range) 46 y (23-64)	MMRD	2%				
	MUD	21%				
Med Dx to SCT (range) 4.2 y (0.6-17.3 y)	MMUD	17%				
Med Chemo Regimens (range) 5 (2-7)	PB (83%) or BM Allogeneic SCT					
[82]	*Prior Auto SCT*	75%	*Diagnoses*		[3.8 y (0.5-5.8 y)]	
Rezvani 2008			Relapsed DLBCL (n = 31)	97%		
	Conditioning		Burkitt (n = 1)	3%		
2+	Flu + 2 Gy TBI	91%			3-year NRM	25%
	2 Gy TBI	9%	*Disease Status at SCT*			
1996-2006			CR	44%	3-year PFS	35%

(*Continued*)

Appendix D. (*Continued*)

Study Design					Patient Outcomes	
[Ref #], Qual. & Strength of Evidence,* and Patient Population	Protocol		Disease and Transplant Characteristics		Follow-Up [Med (Range)] & Patient Outcomes	
Multictr (11)	*Donors*		PR	28%		
Prospective	MRD	66%	Refractory	28%	3-year OS	45%
n = 32	MUD	25%				
	MMUD	9%	*Chemosensitivity at SCT*		3-year Relapse	41%
Med Age (range) 52 y (18-67)			Sensitive	72%		
	PB (97%) or BM		Resistant	28%		
Med Dx to SCT (range) 3.4 y (0.6–7.9 y)	Allogeneic SCT					
			BM Involvement at SCT	6%		
Med Chemo Regs (range) 4 (2-7)						

Allo indicates allogeneic; ATG, antithymocyte globulin; Auto; autologous; Bu, busulfan; CBV, cyclophosphamide/carmustine/etoposide; CI, 95% confidence interval; CR, complete remission; Cy, cyclosphosphamide; DLBCL, diffuse large B cell lymphoma; Dx, diagnosis; EFS, event-free survival; HLA, human leukocyte antigen; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MRD, matched-related donor; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; NRM, nonrelapse mortality; PFS, progression-free survival; PS, performance status; Ritux, rituximab; OS, overall survival; RT, radiation therapy; SFGM-TC, Société Française de Greffe de Moelle et de Thérapie Cellulaire; SCT, stem cell transplantation; TBI, total-body irradiation; TRM, treatment-related mortality; Tx, treatment.
*Quality and strength of evidence definitions are listed in Table 1.