Allogeneic Hematopoietic Cell Transplantation for DLBCL: Who, When and How ?

Speaker: 盧介聖 醫師
Supervisor: 劉峻宇 醫師
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Case

- A 65-year-old man was diagnosed diffuse large B cell lymphoma on 2013/8/7, with the initial presentation of neck mass. (Ann Arbor stage III, IPI: 3, ECOG: 1)
  ➔R-CHOP 4 cycles, 2013/8/23-2013/10/21
  ➔R-ESHAP 1 cycle, 2013/11/22
  ➔R-ICE 1 cycle, 2013/12/17
  ➔R-GemOx 2 cycles, 2013/12/30-2014/1/17
  ➔still PD….

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REVIEW

Allogeneic hematopoietic cell transplantation for diffuse large B cell lymphoma: who, when and how?

E Klyuchnikov[1], U Bacher[1,2], T Kroll[3], TC Shea[4], HM Lazarus[5], C Bredeson[6] and TS Fenske[3]

Despite overall improvements in outcomes of patients with diffuse large B cell lymphoma (DLBCL), ~30–40% of patients develop relapsed or refractory disease. For patients with chemo refractory disease, or recurrent disease following autologous hematopoietic SCT (auto-HCT), the prognosis is poor, with no consensus on the optimal therapy. Currently, owing to the graft vs lymphoma effect, hematopoietic allogeneic hematopoietic cell transplantation (allo-HCT) is the only potentially curative option for such patients. In addition, many patients who are considered today for auto-HCT actually have a low likelihood of benefit. For example, a patient with prior rituximab exposure who relapses within 1 year of diagnosis and has a second-line age-adjusted International Prognosis Index of 2 or 3 at relapse has a <25% chance of being cured by auto-HCT. It is possible that such patients may be better served with an allo-HCT. Unfortunately, in many cases, allo-HCT applicability is limited by patient age, comorbidities, performance status and treatment-related toxicities. Recent attempts to improve the efficacy of auto-HCT, such as incorporating radio-immunotherapy into the conditioning regimen, have not resulted in improved outcomes. However, incorporation of novel agents such as anti-programmed death-1 antibodies as maintenance therapy after auto-HCT show promise. Allo-HCT in relapsed/refractory DLBCL patients can result in a 30–40% PFS rate at 3 years, in part due to a graft vs DLBCL effect. While reduced-intensity/non-myeloablative conditioning is increasingly being used, certain patients may benefit from myeloablative conditioning. We present an algorithm intended to discriminate which relapsed and refractory DLBCL patients are most likely to benefit from auto-HCT vs allo-HCT. New approaches, using novel agents that target the molecular heterogeneity in DLBCL, will be an essential component of moving the field forward. Lastly, we propose a prospective registry-based study as the only feasible mechanism to define the optimal position of allo-HCT in the overall treatment strategy for DLBCL. It is hoped that this review will promote the development of prospective multicenter efforts to determine whether such patients do, in fact, benefit from earlier and/or more effective implementation of allo-HCT.

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Keywords: diffuse large B cell lymphoma; allogeneic hematopoietic cell transplantation; myeloablative conditioning; reduced-intensity conditioning

Introduction

- Despite overall improvements in outcomes of patients with diffuse large B cell lymphoma (DLBCL), ~ 30–40% of patients develop relapsed or refractory disease.
- After failure of auto-HCT, allogeneic HCT offers the benefits of a tumor-free graft and the potential for a graft vs lymphoma (GVL) effect.

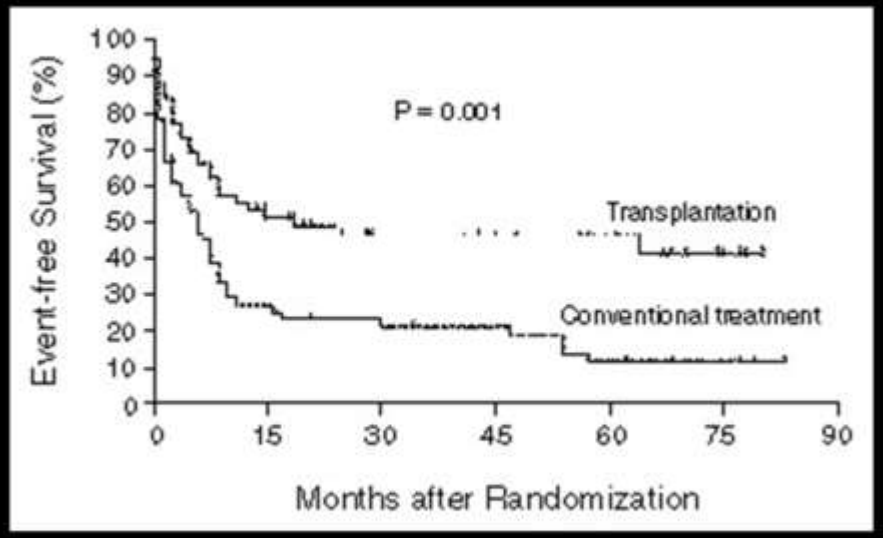
Introduction

- For some patients with a low chance of success with auto-HCT, allo-HCT may represent a superior therapeutic option.
- The authors discuss an new algorithm in relapsed and refractory DLBCL patients unlikely to benefit from auto-HCT, for whom allo-HCT would be a reasonable alternative.

Current Standard of Care for Relapsed and Refractory DLBCL

- **1995 PARMA study**: improved EFS and OS of auto-HCT vs conventional salvage therapy alone for patients with relapsed, chemotherapy responsive, aggressive non-Hodgkin lymphoma.

Kaplan–Meier Curves for Event-free Survival of Patients in the Transplantation and Conventional-Treatment Groups.



Philip T et al. N Engl J Med 1995;333:1540-1545.

The NEW ENGLAND JOURNAL of MEDICINE

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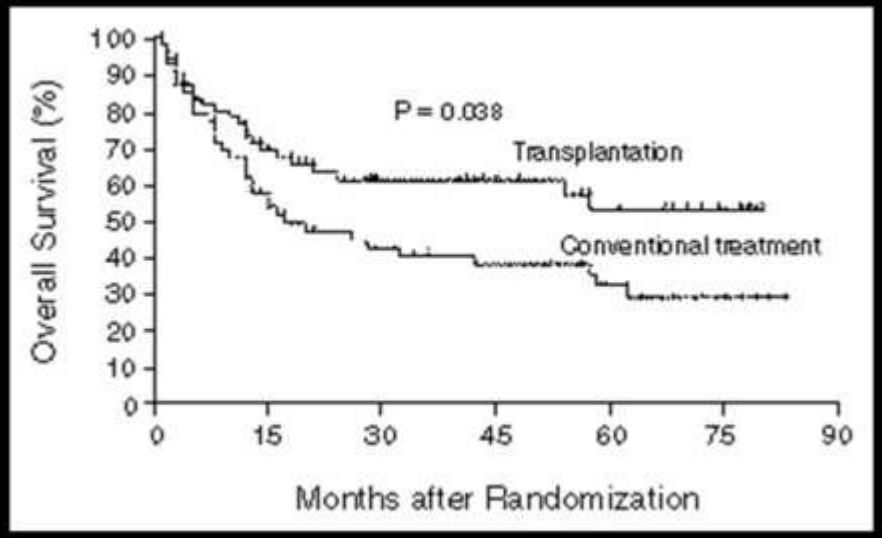

Philip T et al. N Engl J Med 1995;333:1540-1545.

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Current Standard of Care for Relapsed and Refractory DLBCL

PARMA study:

- With auto-HCT, a 5-year EFS of 46% and 5-year OS of 53% .
- Auto-HCT as a standard of care for transplant-eligible patients who have relapsed, chemosensitive DLBCL.

Current Standard of Care for Relapsed and Refractory DLBCL

- 2010 CORAL study:
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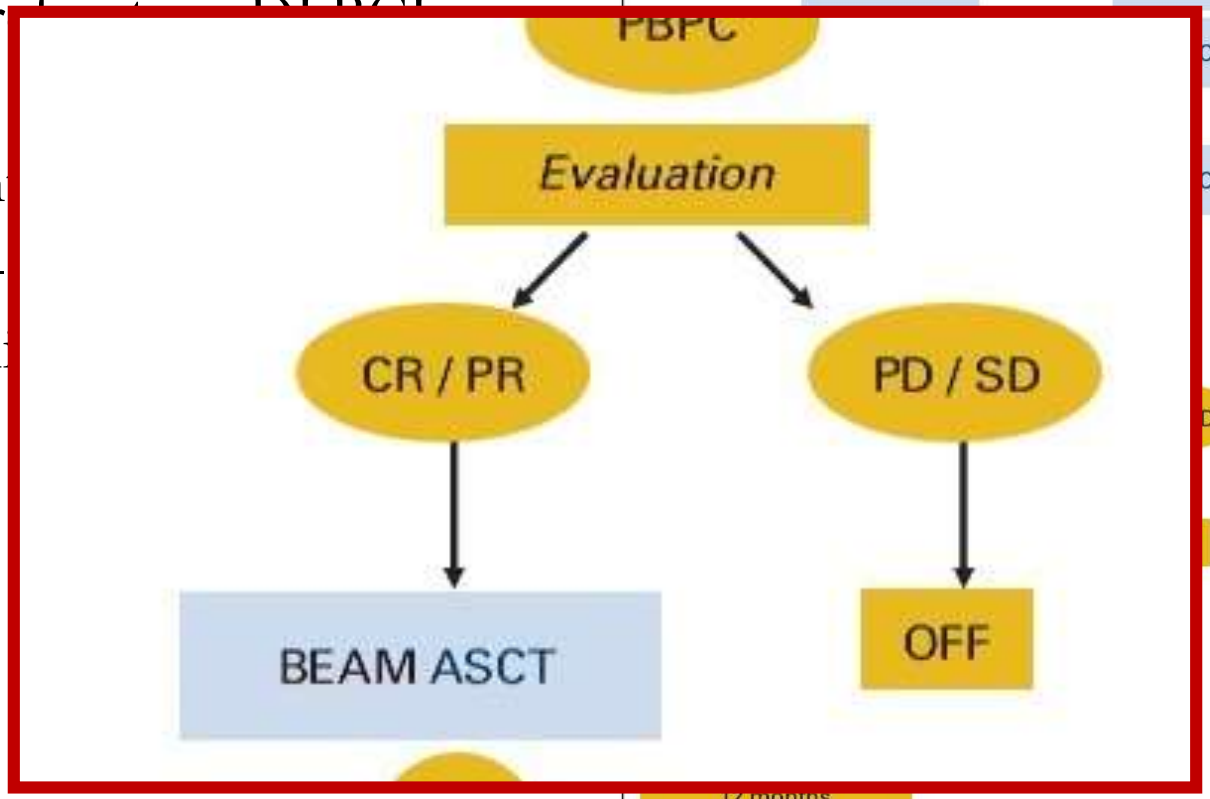
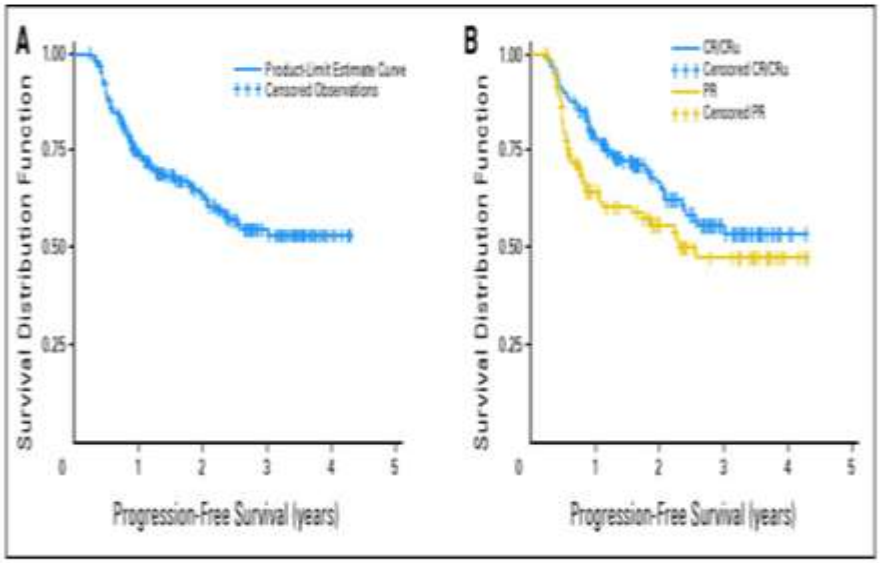


Current Standard of Care for Relapsed and Refractory DLBCL

CORAL study:

- Under auto-HCT, 3-year PFS: 53%.
- A very poor risk group➔ Small chance of benefitting from traditional auto-HCT.



Gisselbrecht C et al. JCO 2010;28:4184-4190

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Current Standard of Care for Relapsed and Refractory DLBCL

Poor risk groups :

- Relapse/progress within 1 year of diagnosis
- A high second-line aaIPI (age-adjusted International Prognostic Index)

Current Standard of Care for Relapsed and Refractory DLBCL

- Several approaches were taken in this regard:
  (1) Modification of the salvage therapy regimen
  (2) Alteration of the auto-HCT-conditioning regimen
  (3) Post-transplant consolidation or maintenance therapy
  (4) Introduction of new or novel agents
  (5) A more extensive or effective use of allo-HCT
  or some combination of above approaches…

Current Standard of Care for Relapsed and Refractory DLBCL

(1) Modification of the salvage therapy regimen:

- ✓ CORAL study: no benefit of one salvage regimen (R-ICE) over another (R-DHAP).
- ✓ 2011 Thieblemont C et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory DLBCL.
- ✓ 2009 Dunleavy K et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma.

Current Standard of Care for Relapsed and Refractory DLBCL

(2) Alteration of the auto-HCT-conditioning regimen:

- ✓ Bu–Cy–E (busulfan, cyclophosphamide and etoposide), with no obvious benefit over BEAM.
- ✓ Adding radio-immunotherapy to traditional BEAM ➔ the Bone Marrow Transplantation Clinical Trials Network (BMT CTN 0401) showed no benefit of adding 131-Iodine tositumomab to standard BEAM, compared with BEAM plus rituximab.

Current Standard of Care for Relapsed and Refractory DLBCL

(3) Post-auto-HCT consolidation or maintenance:

- ✓ CORAL study: no benefit to post-transplant maintenance rituximab.
- ✓ A recent non-randomized study used the anti-programmed death-1 Ab CT-011 (novel targeted therapy), following auto-HCT (18-month PFS of 69%).

Current Standard of Care for Relapsed and Refractory DLBCL

(4) Introduction of new or novel agents:

- ✓ Because of the molecular heterogeneity of DLBCL, it is unlikely that single 'targeted' therapy will dramatically alter the natural history of relapsed and refractory DLBCL.

Table 1. Activity of new/novel agents and regimens in recent relapsed and refractory DLBCL trials

Class	*Agent*	*No. of Patients*	*ORR (%)*	*CR/CRu (%)*	*Median DOR/PFS (months)*
Chemotherapy	GEMOX-R[21]	32	43	34	9.1
	Bendamustine + R[32]	59	63	37	6.5
	DA-EPOCH-B[12]	12[a]	83[a]	41[a]	10.8[a]
Immunomodulators	Lenalidomide[29]	108	30	8	4.6
	Lenalidomide (non-GCB pts)[30]	17[a]	53[a]	24[a]	6.2[a]
mTOR inhibitors	Everolimus + R[28]	25	24	8	11
	Temsirolimus[27]	27	28	12	2.6
Kinase inhibitors	Fostamatinib (Syk inhibitor)[26]	23	22	1	2.7
	Ibrutinib (BTK inhibitor)[33]	25[a]	40[a]	8[a]	5.5[a]
MoAB	Dacetuzumab (anti-CD40)[22]	50	12	2	NA
	Dacetuzumab + R[35]	30	47	20	NA
	Ofatumomab (anti-CD20)[25]	81	11	4	6.9
	Obinutuzumab (anti-CD20)[24]	25	29	NA	2–3 (Varied with dose)
Ab/toxin conjugates	Brentuximab (anti-CD30)[31]	19	47	16	NA
	Inotuzumab ozogamicin (anti-CD20)[23]	25	15	NA	1.5
	Inotuzumab ozogamicin + R[34]	42	74	50	17.1

Abbreviations: ABC = activated B cell; BTK = Bruton's tyrosine kinase; CR/Cru = complete response and complete response, uncomfirmed; DOR = duration of response; GCB = germinal center B cell; GEMOX = gemcitabine + oxaliplatin; mTOR = mammalian target of rapamycin; NA = not assessed; ORR = overall response rate; R = rituximab. [a]Results displayed are restricted to ABC-type DLBCL patients.

Retrospective Comparisons of Allo-HCT and Auto-HCT

- Comparative studies of auto-HCT vs allo-HCT have reported either no significant difference in survival between the two transplant modalities, or an inferior survival in the allo-HCT cohort.

Selection bias !!

Retrospective Comparisons of Allo-HCT and Auto-HCT

- Allo-HCT clearly carries a higher rate of NRM (20–45% at 1–5 years), and this risk increases with a higher intensity of the conditioning regimen, increasing age and declining performance status.
- As a significantly greater proportion of high-risk patients undergo allo-HCT, it is encouraging that the rate of relapse or progression observed after allo-HCT (25–41% at 3–5 years) has been similar to that in patients undergoing auto-HCT (30–40% at 3–5 years).

Are There Patients for Whom Allo-HCT Should Be Chosen Instead of Auto-HCT?

- Given the low anticipated chance for success with auto-HCT in many cases, such as those with rapid relapse and/or high second-line aaIPI after first-line rituximab-containing therapy, the benefits of allo-HCT compared with auto-HCT may outweigh the risks for some of these high-risk patients.

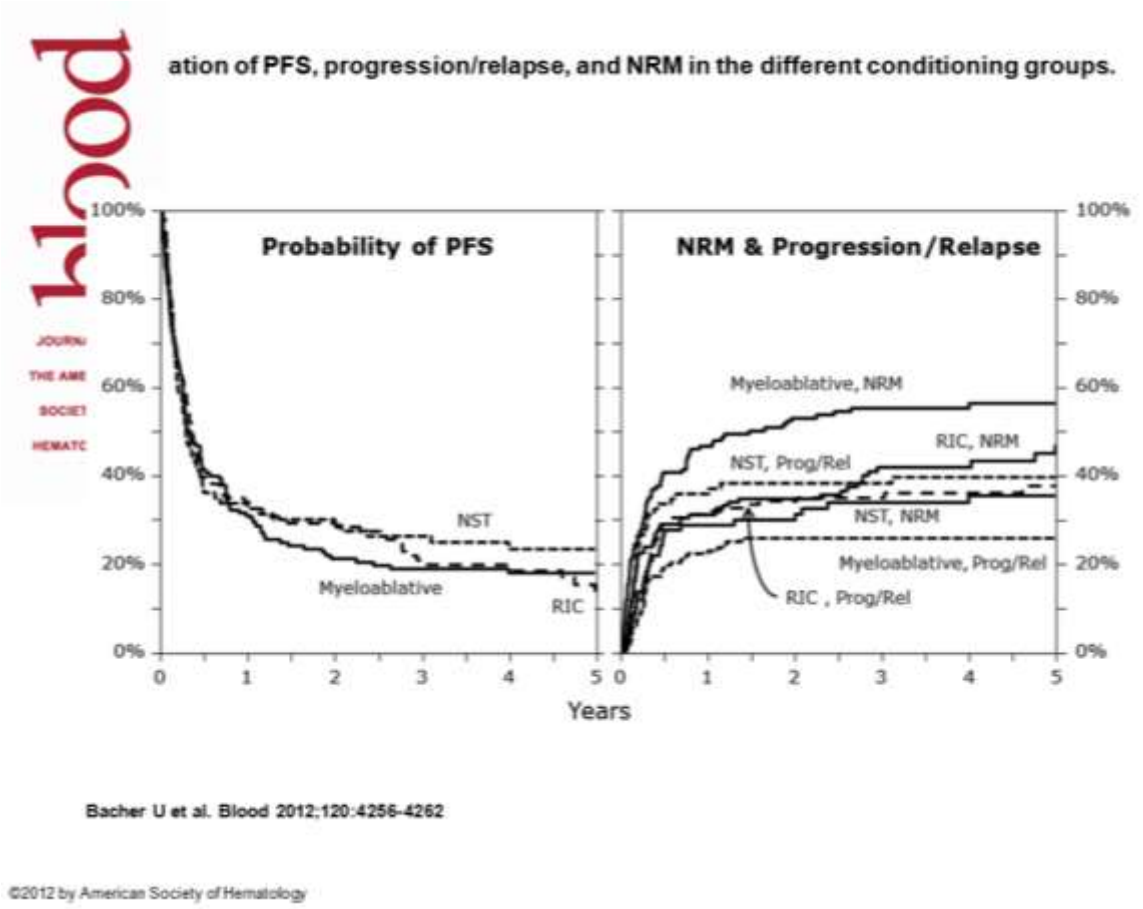
Evidence of a Graft VS DLBCL Effect by Allo-HCT

- GVL effect: regression of lymphoma documented after withdrawal of immunosuppression or after DLI.
- Additional evidence of GVL effect: lower relapse rates in recipients of allografts compared with those undergoing auto-HCT and/or decreased relapse rates in patients who develop chronic GVHD.

Evidence of a Graft VS DLBCL Effect by Allo-HCT

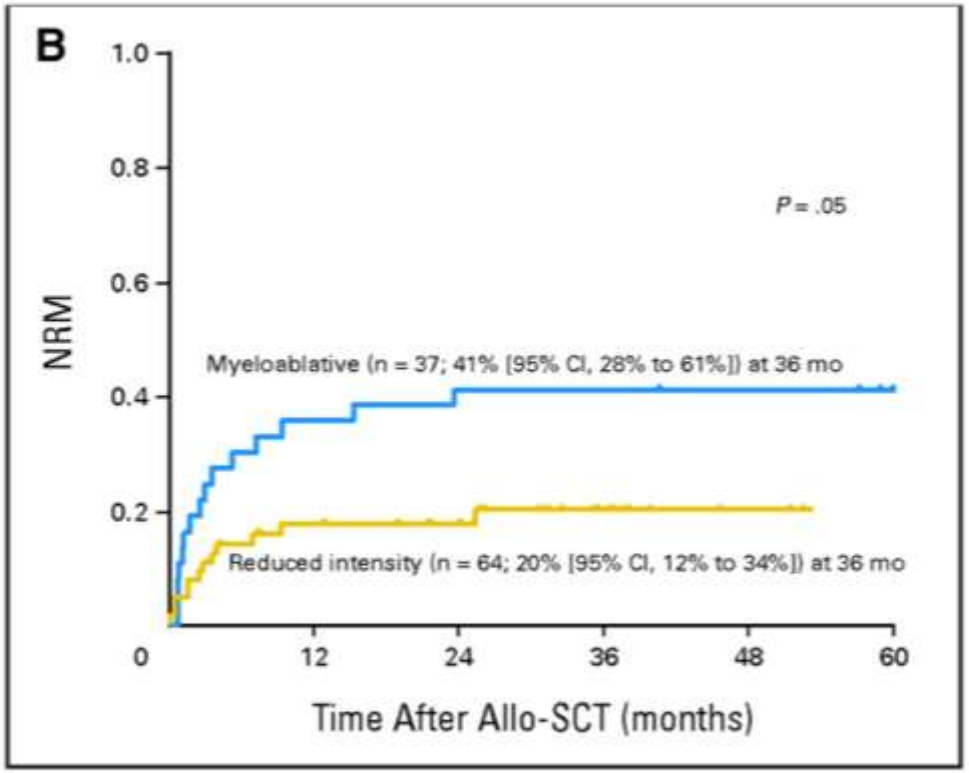
- 2008 Bishop et al. : 18 relapsed/refractory DLBCL under Allo-HCT, 15 patients not in CR on day +100, withdrawal of immunosuppression or DLI alone, response seen in 9 patients and 5 responders developed GVHD, 6 of the 9 responders alive in remission after a median follow-up of 68 months.
- 2009 Thomson et al.: 5/12 patients showing responses(remissions) following DLI.
- 2010 Sirvent et al.: decreased relapse incidence in DLBCL patients who developed chronic GVHD (relative risk of 0.47, with P=0.09).

Impact of Pre-transplant Conditioning



Bacher U, Klyuchnikov E, Le-Rademacher J, Carreras J, Armand P, Bishop MR et al. Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? Blood 2012; 120: 4256–4262.

Impact of Pre-transplant Conditioning



van Kampen R J et al. JCO 2011;29:1342-1348

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van Kampen RJ, Canals C, Schouten HC, Nagler A, Thomson KJ, Vernant JP et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol 2011; 29: 1342–1348

Impact of Pre-transplant Conditioning

Table 2. Transplant outcomes for DLBCL patients after allo-HCT in recent studies

Reference	N	*Median age, years (range)*	*Prior auto-HCT (%)*	*Rituximab prior to allo-HCT (%)*	*Resistant disease at allo-HCT (%)*	*Donor type*	*Conditioning*	*NRM/ TRM (%) (years)*	*Relapse (%) (years)*	*OS (%)*	*PFS (%)*
Rezvani *et al.*[1]	32	52 (18–67)	75	NA	72	MRD, 66%/URD, 34%	**NMAC**: Flu+TBI 2 Gy (91%)	25 (3)	41 (3)	45 (3)	35 (3)
Thomson *et al.*[2]	48	46 (23–64)	71	56	17	MRD, 62%/URD, 38%	**RIC**: Flu+MEL+Alemtuzumab	32 (4)	33 (4)	47 (4)	48 (4)
Sirvent *et al.*[3]	68	48 (17–66)	79 (incl. allo-HCT)	40	19	MRD, 82%/URD, 18%	**RIC**: Flu+BU/+CY/+MEL (74%) **NMAC**: Flu+TBI 2 Gy (24%)	23 (1)	41 (2)	49 (2)	44 (2)
Lazarus *et al.*[7]	79	46 (21–59)	0	NA	42	MRD, 100%	**MAC**: CY+TBI (12 Gy)/+BU (82%)	45 (5)	33 (5)	22 (5)	22 (5)
van Kampen *et al.*[4]	101	46 (18–66)	100	19	26	MRD, 71%/URD, 29%	**MAC**: CY+TBI (12 Gy) ± Eto/+BU (67%) **RIC**: Flu+MEL/+BU/ +CY+Thio (71%)	28 (3) MAC: 41\ RIC: 20	30 (3)	52 (3)	42 (3)
Rigacci *et al.*[6]	165	43 (16–65)	100	NA	33	MRD, 65%/URD, 35%	**MAC** (30%): TBI-based **RIC** (70%): Flu-based	28	25	39 (5)	31 (5)
Bacher *et al.*[5]	396	48 (18–69)	32	67	36	MRD, 33%/URD, 67%	**MAC**: CY+TBI (12 Gy)/+BU (77%) **RIC**: Flu+MEL/+BU (83%) **NMAC**: Flu+TBI 2 Gy/+CY (81%)	56 (5) 47 (5) 36 (5)	26 (5) 38 (5) 40 (5)	18 20 26	18 (5) 15 (5) 25 (5)

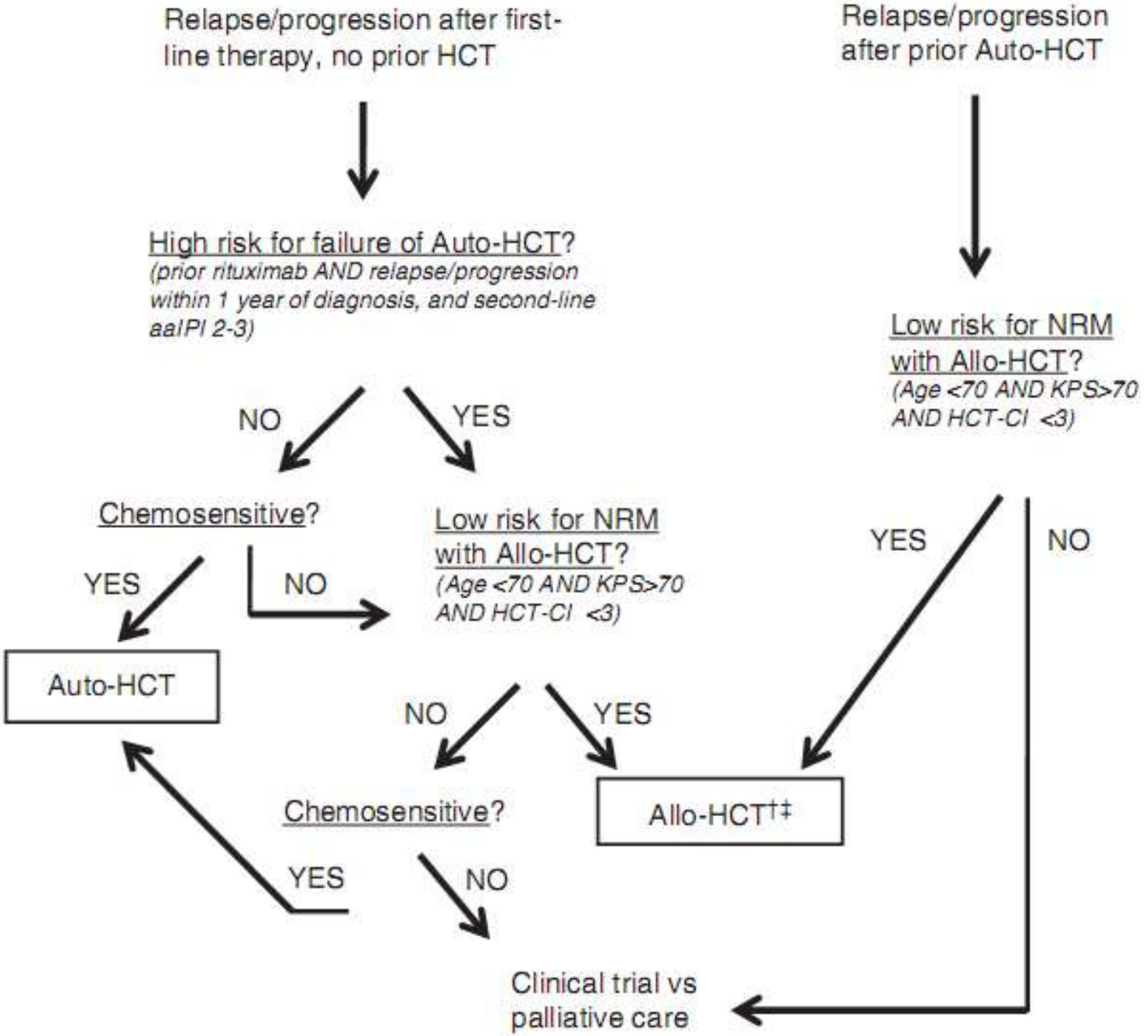
Abbreviations: allo-HCT = allogeneic cell transplantation; auto-HCT = autologous hematopoietic cell transplantation; Eto = etoposide; Flu = fludarabine; MAC = myeloablative conditioning; MEL = melphalan; MRD = matched related donor; N = number of patients; NA = not available; NMAC = non-myeloablative conditioning; NRM = non-relapsed mortality; PD = progressive disease; RIC = reduced-intensity conditioning; SD = stable disease; Thio = thiotepa; TRM = treatment-related mortality; URD = unrelated donor.

Impact of Pre-transplant Conditioning

- MAC has been associated with increased NRM and (in some reports) decreased relapse incidence, compared with RIC.
- MAC allo-HCT seems to have no clear OS advantage over RIC.

Impact of Pre-transplant Conditioning

- For the subgroup of DLBCL patients who are young and fit, with high-risk disease, it is logical (although not yet proven) that MAC may afford better disease control vs RIC, without as much increase in NRM risk.
- For older DLBCL patients, those with comorbid conditions, or those with prior auto-HCT, RIC or NMAC appears to be the better option.
- For younger, fit patients with high-risk disease who achieve a CR prior to allo-HCT, RIC may also be preferred owing to a lower NRM than MAC.

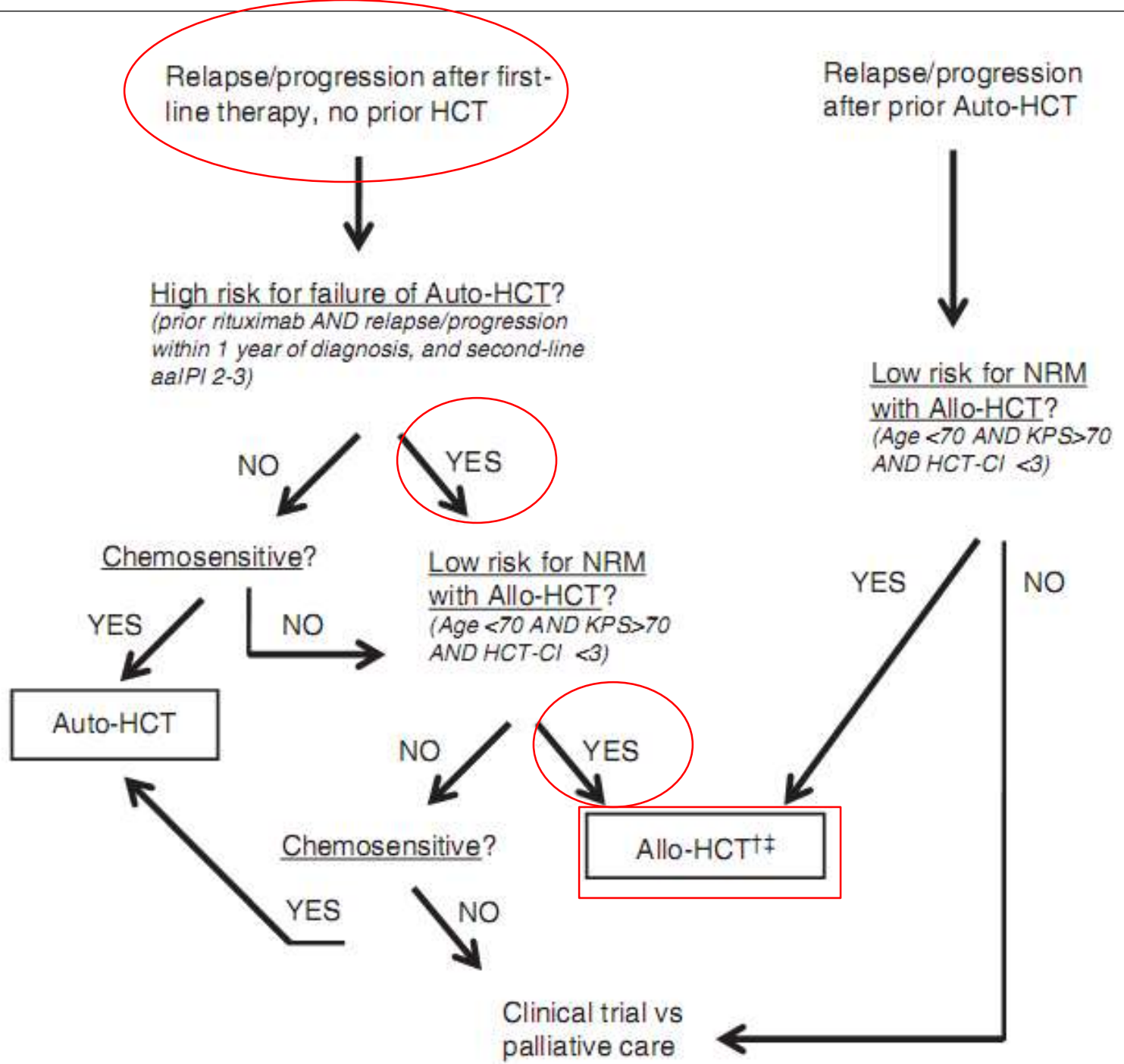

Relapse/progression after first-line therapy, no prior HCT
Relapse/progression after prior Auto-HCT
High risk for failure of Auto-HCT?
(prior rituximab AND relapse/progression within 1 year of diagnosis, and second-line aaIPI 2-3)
Low risk for NRM with Allo-HCT?
(Age <70 AND KPS>70 AND HCT-CI <3)
NO
YES
Chemosensitive?
Low risk for NRM with Allo-HCT?
(Age <70 AND KPS>70 AND HCT-CI <3)
YES
NO
YES
NO
Auto-HCT
NO
YES
Chemosensitive?
Allo-HCT†‡
YES
NO
Clinical trial vs palliative care

Conclusion and Perspectives

- Given the evidence for a GVL effect in DLBCL, combined with the disappointing outcomes for 'high-risk' patients with auto-HCT, we propose that a more extensive use of allo-HCT may translate to improved outcomes for patients with relapsed and refractory DLBCL.

Conclusion and Perspectives

- The authors present an algorithm intended to discriminate which relapsed and refractory DLBCL patients are most likely to benefit from auto-HCT vs allo-HCT.
- New approaches, using novel agents that target the molecular heterogeneity in DLBCL, will be an essential component of moving the field forward.
- The authors also propose a prospective registry-based study as the only feasible mechanism to define the optimal position of allo-HCT in the overall treatment strategy for DLBCL.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YES
NO
Auto-HCT
NO
YES
Chemosensitive?
Allo-HCT†‡
YES
NO
Clinical trial vs palliative care

Thanks for Your Attention!!

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HighWire

Peripheral blood stem cells	119 (72%)	115 (80%)	75 (85%)	
Conditioning regimens				
MAC				
CY/TBI	90 (55%)	0	0	
BU/CY	38 (23%)	0	0	
Bu/MEL	6 (4%)	0	0	
FLU/MEL	4 (2%)	0	0	
FLU/BU	15 (9%)	0	0	
MEL 200	1 (1%)	0	0	
RIC				
BU/CY-low dose	0	2 (1%)	0	
FLU/MEL-low dose	0	44 (31%)	0	
FLU/BU-low dose	0	49 (34%)	0	
CY/VP16 ± BU	0	11 (8%)	0	
FLU/ATG	0	1 (1%)	0	
BEAM + similar	0	17 (12%)	0	
TBI based-RIC per center	0	3 (2%)	0	
TBI-low dose-RIC per center	0	7 (5%)	0	
NMAC				
TBI based	0	0	4 (5%)	
TBI-low dose	0	0	29 (33%)	
FLU/CY	0	0	42 (48%)	
Others				
Other/unspecified	11 (7%)	9 (6%)	13 (15%)	
TBI in conditioning	90 (55%)	15 (10%)	33 (38%)	< .001

Bacher U, Klyuchnikov E, Le-Rademacher J, Carreras J, Armand P, Bishop MR et al. Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? Blood 2012; 120: 4256–4262.

Use this calculator to identify comorbidities in the allogeneic stem cell transplantation population and to enable risk assessment before allogeneic transplant using the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI).

Choose which of the following co-morbitidies apply to your patient.

Hepatic disease (choose one)

- (•) None
- ( ) Mild (chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN)
- ( ) Moderate or severe (cirrhosis, bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN)

Pulmonary disease (choose one)

- (•) None or mild disease
- ( ) Moderate pulmonary (DLCO and/or FEV1 66% to 80% or dyspnea on slight activity)
- ( ) Severe pulmonary (DLCO and/or FEV1 = 65% or dyspnea at rest or requiring oxygen)

Other factors

- [ ] Arrhythmia (Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias)
- [ ] Cardiac (CAD, CHD, myocardial infarction or ejection fraction = 50%)
- [ ] Inflammatory bowel disease (Crohn's or ulcerative colitis)
- [ ] Diabetes (requiring insulin or oral hypoglycemics)
- [ ] Psychiatric disturbance (depression or anxiety requiring psychiatric consult or treatment)
- [ ] Obesity (body mass index > 35 kg/m^2)
- [ ] Infection (requiring continuation of antimicrobial treatment after day 0)
- [ ] Cerebrovascular disease (TIA or cerebrovascular accident)
- [ ] Rheumatologic (SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica)
- [ ] Peptic ulcer (requiring treatment)
- [ ] Moderate or severe renal failure (serum Cr > 2 mg/dL or 177 µmol/L, dialysis, or prior renal transplant)
- [ ] Prior solid tumor (excluding nonmelanoma skin cancer)
- [ ] Valvular Heart Disease (except mitral valve prolapse)

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