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How I manage patients with relapsed/refractory diffuse large B cell lymphoma

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Summary

Despite progress in the upfront treatment of diffuse large B cell lymphoma (DLBCL), patients still experience relapses. Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard second-line treatment for relapsed and refractory (R/R) DLBCL. However, half of the patients will not be eligible for transplantation due to ineffective salvage treatment, and the other half will relapse after ASCT. In randomized studies, no salvage chemotherapy regimen is superior to another. The outcomes are affected by the secondary International Prognostic Index at relapse and various biological factors. The strategy is less clear in patients who require third-line treatment. A multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study conducted in 636 patients with refractory DLBCL showed an objective response rate of 26% (complete response 7%) to the next line of therapy with a median overall survival of 6·3 months. In the case of a response followed by transplantation, long-term survival can be achieved in DLBCL patients. There is clearly a need for new drugs that improve salvage efficacy. Encouraging results have been reported with chimeric antigen receptor -T cell engineering, warranting further studies in a well-defined control group of refractory patients. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) was used as a handy framework to build the discussion.

Keywords: refractory/relapsed DLBCL, HSC transplantation, CAR-T cells, chemotherapy, cellular therapies.

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) and can be cured by immunochemotherapy. The current standard of care for the first-line treatment of DLBCL is chemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP), yielding complete and sustained remission in about 60% of cases (Coiffier *et al*, 2002).

The rate of relapse was between 30% and 40% of patients, with an additional 10% present with refractory disease (Coiffier *et al*, 2010). Relapsed DLBCL is characterised by the appearance of any new lesion after a complete response (CR), while refractory DLBCL is defined as the failure of <50% of lesions to be reduced in size following initial treatment, as per the criteria defined by Cheson *et al* (2007). In these clinical settings, the standard therapeutic option is to initiate high-dose therapy (HDT) prior to either autologous or allogeneic stem cell transplantation (ASCT, alloSCT) in chemosensitive patients (Philip *et al*, 1995).

Patients who are ineligible for SCT or who fail after second-line therapy have a poor prognosis (Feugier *et al*, 2005), but recent findings have revealed that they could benefit from alternative salvage therapies (Van Den Neste *et al*, 2016). Salvage therapies may also be used as a bridge to ASCT or allo-SCT.

The aim of this article is to provide guidelines regarding how to manage relapsed or refractory DLBCL (RR-DLBCL), as well as to provide novel strategies in multiple relapsed DLBCL.

We consider different issues: factors affecting survival, type of salvage regimen, type of conditioning regimen, treatment post-ASCT and strategies for patients who do respond to the first salvage regimen or who relapse after transplantation.

How to manage patients at the first relapse

A new biopsy is necessary and new staging with positron emission tomography (PET)

Most relapses are detected within the first 2 years by the occurrence of clinical symptoms during the follow-up. Good clinical judgment and a careful history and physical examination are the most important components of monitoring patients after treatment. They should be repeated at regular intervals, focusing on the initial site of the disease. Computed tomography (CT) can be used, but PET scan is not recommended in the absence of a measurable mass to avoid false positives and increased anxiety of the patient and doctor (Cheson *et al*, 2007).

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The relapse rate is related to adverse prognostic factors defined by the International Prognostic Index (IPI), and can reach 50% in the presence of 3 or more factors but is limited to 10–20% in patients with 0–2 factors.

Once the progression is suspected, the clinician in charge of the patient should again organize the procedures for diagnosis and staging. Relapses generally occur in the same site but also at distant ones. A PET scan will rapidly detect the extent of the disease and the bulk of the tumour that will be used as the baseline to determine the response to salvage therapy. The interval between upfront treatment and date of relapse and type of initial chemotherapy will be part of the discussion. Routine biological tests and evaluation of comorbidities (Sorror *et al*, 2005) will classify patients according to the IPI at relapse and whether they are eligible for transplantation and, if so, which type.

A new biopsy is warranted to confirm that the diagnosis is still a DLBCL without discordant histology (Arber & George, 2005; Brudno *et al*, 2016; Kansara *et al*, 2016) with or without a low-grade component. The patient may be reluctant to undergo a new surgical procedure, especially in the abdomen or thorax. Core needle biopsy is performed more frequently and uses a large gauge needle, allowing diagnosis in 90% of cases without surgical procedures (de Kerviler *et al*, 2000). Several cores are recommended to allow the detection of biological markers of interest (de Kerviler *et al*, 2012).

Diffuse large B cell lymphoma currently comprises several entities described by gene profiling technology and gene sequencing. However, not all of them are important for clinicians if the patient is cured. However, in the case of relapse or refractory disease, they can facilitate targeting therapy. The main biological subtypes defined in the World Health Organization 2016 classification for DLBCL are the germinal centre B lymphocytes (GCB) and non-GCB subtypes (Swerdlow *et al*, 2016) which are better determined by gene expression profiling. Non-GCB lymphoma, which could be detected routinely by well standardized immunohistochemistry according to the Hans algorithm, has a worse prognosis (Hans *et al*, 2004). This distinction can also provide some insights concerning pathway abnormalities, suggesting different modes of action of antineoplastic drugs. For instance, combination chemotherapy with rituximab-dexamethasone, cytarabine and cisplatin (R-DHAP) was more effective in the GCB subtypes than the rituximab-ifosfamide, etoposide, and carboplatin (R-ICE) regimen (Thieblemont *et al*, 2011). Some other drugs, such as ibrutinib or lenalidomide, seem to be more active in the non-GCB subtype.

Some other markers, such as the chromosomal break point *MYC*/8q24 translocation or *BCL2*, are associated with an even poorer prognosis at diagnosis and at relapse (Cuccuini *et al*, 2012). They are present in 10 to 20% of DLBCL cases. Unfortunately, there is no actively designed drug specifically for this group of patients, and it is unclear whether alloSCT should be preferred to ASCT (Herrera *et al*, 2018). Other translocations can be associated with a subset of DLBCL, such as primary mediastinal B lymphoma (PMBL). The 9p24.1 translocation found in PMBL, especially in grey-zone lymphoma, is associated with a dramatic response rate to the immune checkpoint inhibitor anti-PD1 (also termed anti-PDCD1) (Melani *et al*, 2017), providing a good example of the evolution of biology related to targeted treatment. With the development of new technologies, such as whole-exome sequencing, it will be possible to reveal novel disease drivers and risk groups (Reddy *et al*, 2017) and design more rational targeted therapy (Sehn & Gascoyne, 2015).

Is there a better salvage regimen?

One of the major rules for consolidation with high-dose therapy and ASCT is its application only in patients in complete or good partial remission after salvage chemotherapy, with adequate collection of stem cells.

There are many salvage therapies available, mostly involving rituximab in combination with standard antineoplastic agents. The most frequently used combinations are as follows (Sehn & Gascoyne, 2015):

- R-ICE = rituximab plus ifosfamide, carboplatin and etoposide
- R-DHAP = rituximab plus cytosine, arabinoside, cisplatin and dexamethasone
- R-GDP = rituximab plus gemcitabine, dexamethasone, cisplatin
- R-ESHAP = rituximab plus etoposide, methylprednisolone, cytarabine, cisplatin
- R-GemOx = rituximab plus gemcitabine and oxaliplatin (R-GemOx)

The best chemotherapy regimens are those that provide the highest response rates with the most tolerable toxicity. There remains no clear evidence regarding the superiority of one regimen over another in randomized studies. Failure to collect peripheral stem cells is around 10% and does not seem, in the first relapse, to be different from one regimen to another (Gisselbrecht *et al*, 2010).

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was a phase III, multicentre, randomized trial that compared the efficacy of 3 R-ICE or R-DHAP cycles followed by ASCT with or without rituximab maintenance in patients aged 18–65 years with previously treated DLBCL. Several messages can be drawn from this randomized study, the first in the rituximab era (Fig 1) (Gisselbrecht *et al*, 2010, 2012).

In this study, the 48-month overall survival (OS) was 48%. There was no difference between the two rituximab-containing salvage regimens, R-DHAP in 234 patients and R-ICE in 243 patients. Overall, only 50% of the patients could proceed to ASCT, mainly because of an insufficient response to second-line treatment. The rate of collection failure of stem cells was 10% in both arms. In the LY 012 randomized

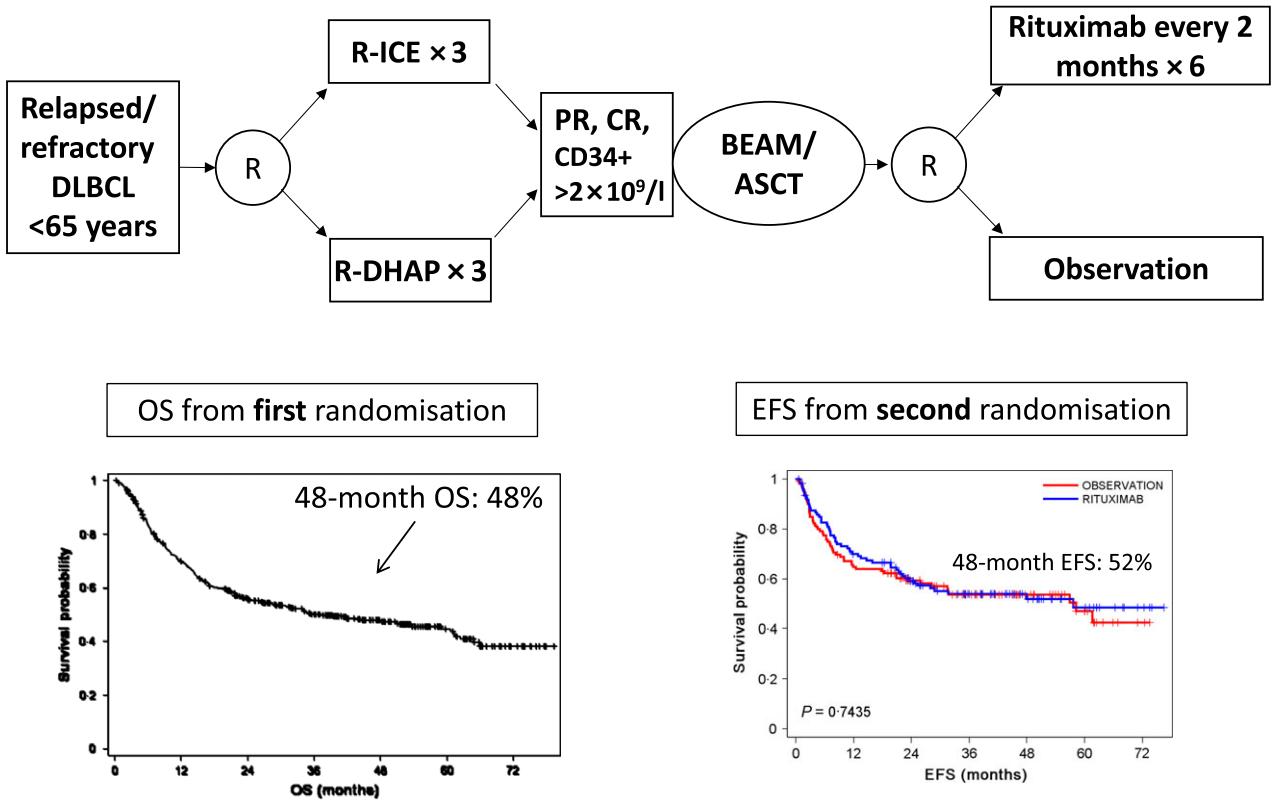

Fig 1. Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study: main results (Gisselbrecht *et al*, 2010, 2012). ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytarabine, melphalan; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; OS, overall survival; PR, partial response; CR, complete response; R-DHAP, rituximab-dexamethasone, cytarabine, cisplatin; R-ICE, rituximab-ifosfamide, etoposide, carboplatin.

study, compared with DHAP as second-line treatment, treatment with gemcitabine, dexamethasone and cisplatinum (GDP) administered prior to high-dose chemotherapy and ASCT was non-inferior but was associated with fewer adverse events, better preservation of the patient-reported quality of life and less frequent hospitalization (Crump *et al*, 2014). However, GDP did not increase the proportion of patients who could proceed to transplantation, a major drawback for 50% of the patients. The substitution of rituximab with another anti CD20, ofatumumab, did not improve the results over RDHAP (van Imhoff *et al*, 2017). Overall, the development of new drugs (Table I) mean that it is unlikely that these three primary regimens (DHAP, ICE and GDP) will remain standards in the future (Gisselbrecht, 2013).

Several phase 2 studies with new drug combinations are ongoing, with mostly disappointing results. Recently, the combination of ibrutinib with R-ICE was reported, with an encouraging response rate of 90% in only 20 patients, warranting a randomized study (Sauter *et al*, 2018).

Nevertheless, the addition of rituximab to second-line chemotherapy, followed by ASCT, significantly improved progression-free survival (PFS) in patients not exposed to rituximab as part of their first-line treatment (Vellenga *et al*, 2008).

However, early relapse and prior exposure to rituximab during first-line treatment were associated with a worse outcome. In the latter, the overall response rate (ORR) to salvage regimen was only 46%, and the 2-year PFS was 20% (Gisselbrecht *et al*, 2010). These results agree with the data from a retrospective study on R-ESHAP in patients with or without previous exposure to rituximab (Martin *et al*, 2008).

Hamadani *et al* (2014) reported the analysis of the Center for International Blood & Marrow Transplant Research registry data from two cohorts of transplanted DLBCL who were previously exposed to rituximab, including 300 patients with early relapse (EFR; <12 months) and 216 patients with late relapse (LRF). These patients had achieved either partial response (PR, 267 patients) or CR (249 patients) to salvage chemotherapy before transplantation. The 3-year PFS for the EFR group was 44%, compared with 52% for the LRF group ($P = 0{\cdot}08$). If the PFS for the EFR cohort was inferior, it was only apparent during the initial part of the curve, post-ASCT (<9 months, $P < 0{\cdot}001$); thereafter, the outcome was similar between the two groups. The same observation was described for the 50% 3-year OS of the EFR group *versus* the 67% OS for the LRF group ($P < 0{\cdot}001$). The authors concluded that ASCT provides durable disease control, regardless of the

Table I. Salvage chemotherapy regimens in randomized studies for DLBCL [Gisselbrecht *et al*, 2010 (CORAL study); Crump *et al*, *2014* (LY.12 study); van Imhoff *et al*, 2017 (ORCHARRD study)].

Salvage induction	N	RR	Transplant rate	PFS
R-ICE	202	64%	51%	3-year: 31%
R-DHAP (CORAL)	194	63%	55%	3-year: 42%
(R)-DHAP (LY12)	304	45%	49%	3-year: 28%
(R)-GDP	306	44%	52%	3-year: 28%
R-DHAP (ORCHARRD)	223	42%	37%	2-year: 26%
O-DHAP (ORCHARRD)	222	38%	33%	2-year: 24%

(R)-GDP, (rituximab)-gemcitabine, dexamethasone, cisplatinum; DLBCL, diffuse large B cell lymphoma; O-DHAP, Ofatumumab- dexamethasone, cytarabine, cisplatin; PFS, progression-free survival; R-DHAP, rituximab-dexamethasone, cytarabine, cisplatin; R-ICE, rituximab-ifosfamide, etoposide, carboplatin; RR, relative risk.

timing of relapse in DLBCL patients treated with first-line immunochemotherapy. However, they noted that patients in the EFR group had a higher rate of relapse than the those in the LRF group in the early period (6–9 months) following transplantation.

Because many patients develop disease that is refractory to rituximab, the available evidence suggests that its role in salvage therapy should be reconsidered. This challenge should also be overcome by the development of new chemotherapy combinations and novel agents.

Fludeoxyglucose (FDG)-PET scan in evaluating a response

The incorporation of post-salvage PET-CT scans can be used to risk-adapt therapy. The quality of the response prior to ASCT is highly predictive of the outcome. Several groups have shown improved survival for patients with a negative pre-ASCT PET-CT; this has been confirmed in a previously reported meta-analysis (Filmont *et al*, 2007; Terasawa *et al*, 2010). Interestingly, and similar to patients with Hodgkin lymphoma, patients with FDG-avid disease pre-ASCT with a Deauville score of 4 have a suboptimal outcome, but approximately 40% of patients can still be cured using this approach (Sauter *et al*, 2015). It is important to remember that these patients still have chemosensitive disease based on CT criteria, and ASCT should not be withheld systematically because their pre-ASCT PET-CT is positive. It is the responsibility of the investigators to adapt transplantation for these patients to improve their cure rate. Obvious research studies for this cohort include novel conditioning regimens or post-transplantation therapy.

In summary, only 50% of relapses are eligible for transplant, and half of them will relapse after transplant. This figure should be adapted to prognostic factors and only patients who are transplanted. A secondary IPI score of 2–3 at relapse was the main factor in multivariate analysis (OS: Hazard ratio: 2·252; *P*: 0·0004), which is even more important than an early relapse at <12 months or prior rituximab exposure (Gisselbrecht *et al*, 2012).

Do we need adjuvant treatment post transplantation?

In the subpopulation of the CORAL study that underwent ASCT, 122 patients received 1-year maintenance treatment with rituximab, and 120 patients were assigned to observation only (Gisselbrecht *et al*, 2012). At 4 years, no difference in EFS was observed between the rituximab maintenance group and control group (52% vs. 53%, respectively), although there was a 15% attributable risk of serious adverse events (SAEs) in the active therapy group.

The rate of relapse was over 40%, and rituximab maintenance could not reduce this rate in transformed histology included in the Canadian study (Kuruvilla *et al*, 2015). Rituximab is therefore not recommended as a maintenance therapy after ASCT. Other agents active in DLBCL are under evaluation but will need completed randomized studies before going in clinical practice.

The role of consolidative (involved) local radiotherapy has been proposed pre-transplantation, such as that in the PARMA study (Philip *et al*, 1995), but most studies focus on post-transplantation. No randomized study has been performed, and it is mostly restricted to the residual mass, especially in patients not in CR before transplant with a positive FDG PET scan (Hoppe *et al*, 2009). Positive results have been reported, but there was also a concern about an increase in late toxicities. It should be discussed case-by-case depending on the site and size of the residual tumour.

Can we improve the conditioning regimen pre ASCT?

ASCT is currently a standard treatment in relapsed lymphoma, with BEAM (carmustine, etoposide, cytarabine, melphalan) being the preferred and most widely adapted HDT regimen for transplantation. Apart from specific safety concerns regarding the pulmonary toxicity of carmustine, the limited availability of this drug makes the exploration of possible alternatives to BEAM desirable. A comparison of BEAM with TEAM (thiothepa TT replacing carmustine) implemented by the European

Table II. Overall response rate of new selected single agents in DLBCL patients.

Agent	Target	Status	ORR	DLBCL subtype	References
Ibrutinib	BTK	Phase I/ II	37%	ABC	Wilson *et al* (2015)
Fostamatinib	SYK	Phase II	3%	DLBCL	Flinn *et al* (2016)
			22%		Friedberg *et al* (2010)
Lenalidomide	Immunomodulator	Phase II	42%	DLBCL	Zinzani *et al* (2015)
			52%	ABC	Hernandez-Ilizaliturri *et al* (2011)
Bortezomid + chemotherapy	NF-κB	Phase II	83%	ABC	Dunleavy *et al* (2009)
Tazemetostat	EZH2	Phase II	60%	DLBCL	Italiano *et al* (2018)
Everolimus	mTOR	Phase II	30%	GCB	Witzig *et al* (2011)
Temsirolimus	mTOR	Phase II	28%	DLBCL	Smith *et al* (2010)
CUDC 907	PI3Kδ + HDAC	Phase II	37%	GCB/*MYC*	Oki *et al* (2017)
Bendamustine	Nitrogen mustard/ purine-like	Phase II	44%	DLBCL	Weidmann *et al* (2002)
Obinutuzumab	CD20	Phase II	32%	DLBCL	Morschhauser *et al* (2013)
MOR00208	CD19	Phase II	29%	DLBCL	Jurczak *et al* (2018)
Blinatumumab	B-specific CD19/CD3	Phase II	43%	DLBCL	Viardot *et al* (2016)
Polatuzumab vedotin	CD79b	Phase I	25%	DLBCL	Palanca-Wessels *et al* (2015)
Nivolumab	Anti-PD1	Phase I	36%	DLBCL	Lesokhin *et al* (2016)

ABC, activated B cell; DLBCL, diffuse large B cell lymphoma; GCB, germinal centre B cell; ORR, overall response rate.

Society for Blood and Marrow Transplantation (EBMT) (Sellner *et al*, 2016). TT is an alkylating agent regularly used in conditioning regimens for primary central nervous system lymphoma because of its capacity to cross the blood-brain barrier (Soussain *et al*, 2012).

In the EBMT registry-based retrospective analysis, 535 patients had received a TT-based preparation for ASCT and a comparative study of BEAM- and TT-based preparation could be undertaken. No significant differences for any safety or efficacy end point could be demonstrated between the BEAM- and TT-based regimens for the whole population as well as for relatively large groups of the DLBCL patients (Sellner *et al*, 2016).

In another large registry study comprising 4,917 patients with lymphoma, the outcomes of various commonly used high-dose therapies (BEAM, cyclophosphamide/carmustine/etoposide, busulfan/cyclophosphamide, and total body irradiation-based) revealed that several significant but often only subtle outcome differences between different HDT platforms were found in individual NHL subsets (Chen *et al*, 2015a).

Recently, investigators have incorporated newer agents into traditional high-dose regimens (Vose *et al*, 2013) and have conducted several trials combining 131-Iodine tositumomab with BEAM for ASCT, but no clear advantage was observed in the phase III trial. Other trials have studied the addition of (90)Y-ibritumomab tiuxetan to BEAM conditioning (Gisselbrecht *et al*, 2009). Clearly, prospective randomized trials will determine if the incorporation of these newer agents into HDT regimens has significant value. However, based on our results, the selection of the control needs to consider the differences in outcomes based on histology.

Although HDT and ASCT can offer durable remission in many patients with relapsed or high-risk lymphoma, elderly patients are often not considered suitable candidates due to concerns regarding excess toxicity and mortality. There is no real age limit as long as the patient is still fit. The comorbidity index (Sorror *et al*, 2005) is not completely helpful for eligibility in most of the reported series.

Nevertheless, very few patients aged older than 70 years are found in the registry (Jantunen *et al*, 2008). A retrospective study showed favourable transplant outcomes, including those concerning survival and toxicity, in a large cohort of lymphoma patients aged older than 70 years who underwent ASCT (Sun *et al*, 2018). Eligibility for ASCT should be an individualized decision, and age should not be an absolute contraindication to ASCT in healthy elderly patients with lymphoma.

What is the outcome of patients who fail the first salvage regimen?

Should we try another treatment?

We sought to investigate the characteristics and outcomes of patients who were withdrawn from the CORAL strategy prior to transplantation and who were candidates for third-line treatments off protocol. They received modalities ranging from oral palliative chemotherapy to experimental drugs or intravenous polychemotherapy. Depending on the patient response and local situation, there was sometimes an attempt to consolidate with ASCT or alloSCT (Van Den Neste *et al*, 2016). Among the 203 patients, 170 (83·7%) were removed from the CORAL salvage strategy with R-DHAP/ICE for an event characterized as "treatment failure", 19 (9·4%) for treatment toxicity, one (0·5%) for major protocol violation and 13 (6·4%) for various other reasons. Thus, some of the 203 patients had a CR (n = 26; PR, n = 30) at the time of CORAL withdrawal.

Among the patients, 57·6% experienced a first-remission duration <12 months. The IPI score at the second failure was mostly 2–3 in 52·2% of the patients. ICE-type, DHAP-like and gemcitabine-containing regimens were administered to 19·5%, 18·9% and 14·5% of the patients, respectively. For evaluable patients, the CR/unconfirmed CR (CRu) and PR rates were 33·1% (55/166) and 14·5% (24/166, 95%), respectively, resulting in an ORR of 47·6%. Responses were observed in all subgroups, even in those with stable or progressive disease. The ORR rate according to the type of third-line regimen was 51·7% after the ICE-type and 41·4% after the DHAP-type. Among patients included in the R-ICE arm of CORAL, 26 received a DHAP-like regimen as third-line therapy, with an ORR of 42·3%. Conversely, in patients who failed R-DHAP, 23 were rescued using an ICE-like regimen as third-line therapy, and 43·5% responded. The median OS of the entire population was 4·4 months, corresponding to a 1- and 2-year OS of 23% and 15·7%, respectively. OS was not significantly different according to the reason for CORAL withdrawal (treatment failure, toxicity and protocol violation, among others).

Among the 203 patients, 64 (31·5%) were eventually transplanted, mostly with ASCT ($n = 56$) but some with allogeneic material ($n = 8$). The transplanted patients had a significantly lower IPI at failure and were better responders after third-line salvage (CR/PR in 68·8%) compared with 31·2% of the non-transplanted patients ($P < 0·001$). The median OS was 11·1 months in patients who were eventually transplanted compared with 3·3 months in those who were not ($P < 0·0001$, log-rank 2·467), corresponding to a 2-year OS of 33·9% and 9·3%, respectively. Interestingly, the median OS was not reached in patients who achieved CR/CRu after a third-line regimen and who received further ASCT (1-year OS of 88·4%, data not shown).

This approach, i.e., salvage chemotherapy aimed to achieve a response followed by transplantation, should be encouraged in these patients, even in the rituximab era.

What is the outcome of refractory DLBCL?

Clinical observations suggest that patients with refractory DLBCL, defined as no response to the last chemotherapy or relapse ≤12 months post-ASCT, have poor overall survival rates; however, there is a paucity of published data reporting outcomes in this patient population. With many promising therapies under development for refractory DLCBL, there is a need for a more precise understanding of the expected response and OS rates with the currently available therapies in this patient population to establish a benchmark for future studies. An international multicohort retrospective NHL research (SCHOLAR-1) study of pooled data from 2 phase III clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence) was conducted to evaluate responses and OS rates in patients with refractory NHL (Crump *et al*, 2017). Among 861 patients with DLBCL and transformed follicular lymphoma (TFL), 636 were included based on refractory inclusion criteria. Patients had refractory, aggressive NHL stable disease for ≤6 months with ≥4 cycles of frontline (28%) or, progressive disease as the best response (50%) following ≥2 cycles of later-line therapy, or relapse ≤12 months post-ASCT (22%).

In SCHOLAR-1 (Crump *et al*, 2017), 64% of the patients were male, and 15% were aged ≥65 years. Among the assessed patients, 73% had an Eastern Cooperative Oncology Group performance score 0–1, 72% had stage III-IV disease, and 33% had an IPI score ≥3. Four percent of the patients had TFL, and 27% had received ≥3 lines of therapy.

For patients with refractory DLBCL, the objective response rate was 26% (CR, 7%) to the next line of therapy, and the median OS was 6·3 months. The outcomes were consistently poor across the patient subgroups and study cohorts. The OS rates were similar regardless of the refractory subgroup, with a slightly lower median OS among patients who were refractory to second-line or later-line therapy or who relapsed ≤12 months post-ASCT (6·1 and 6·2 months, respectively) than among primary refractory patients (7·1 months). Survival in the post-ASCT group was similar to that in the other refractory subgroups evaluated (Crump *et al*, 2017).

However, 20% of patients were alive at 2 years. Although they represented a relatively small proportion of patients, those who achieved a CR after the last salvage chemotherapy had a longer survival (median OS, 14·9 months) than non-responders (median OS, 4·6 months) with a 2-year OS rate of 14%. Thirty-one patients who achieved a CR underwent ASCT, and their median OS was more than 6 years at the time of this analysis. Of the 54 patients who achieved a partial response (PR) and underwent ASCT, the median OS was 17·8 months (Crump *et al*, 2017). These data are particularly important because they represent many patients treated in the modern rituximab era, suggesting that, even with the availability of multiple rituximab-based regimens, the outcomes among patients with refractory DLBCL remain dismal across global centres and trials. The response to therapy was significantly associated with longer survival, particularly in patients who were subsequently submitted to ASCT. However, most patients (73%) did not respond to salvage therapy or could not receive ASCT. There is an urgent unmet need to not only improve salvage regimens that may increase the percentage of patients eligible for SCT but also ideally develop novel and effective therapeutic options to treat this patient population.

Cellular therapy with allogenic transplantation: an alternative in difficult situations

Unlike ASCT, alloSCT generates an allogeneic graft-versus-lymphoma (GvL) effect that reduces the likelihood of disease relapse following transplantation. The advent of reduced-

intensity conditioning (RIC) regimens has renewed interest in alloSCT, which reduces non-relapse mortality while maintaining a GvL effect, thereby allowing the treatment of elderly patients and/or patients with co-morbidities. The availability of matched unrelated donors or haploidentical transplantation has opened the doors for an extension of indications in DLBCL observed in the registry data.

Currently, the major role of reduced-intensity conditioning alloSCT (RIC-allo) is in the treatment of patients who have failed an ASCT or in whom an ASCT is not possible. In the EBMT registry, of 101 patients with DLBCL who had relapsed after ASCT, the 3-year PFS and OS rates post-transplantation were 41% and 52%, respectively (van Kampen *et al*, 2011). A comparison of RIC and myeloablative-conditioning regimens prior to alloSCT revealed no significant differences in PFS or OS. However, there was a trend toward a lower non-related mortality with RIC-allo. The two main factors affecting the outcome were relapse less than 12 months after ASCT and the quality of the response before transplantation. Improvement of the response remains the key issue.

With a better definition of the prognostic factors and poor results obtained with HDT/ASCT in early relapse, high secondary IPI, and double-hit translocation (Herrera *et al*, 2018), we can now discuss whether, in the case of a response, these patients should be transplanted directly with RIC-allo or ASCT or treated with a tandem approach of ASCT followed by RIC-allo (Chen *et al*, 2015b). Nevertheless, it should be underscored again that RIC-allo should not be proposed to refractory patients who are not responding to salvage chemotherapy. The evaluation of such an approach remains an unsolved challenge.

How to manage DLBCL patients who are not eligible for high-dose therapy and ASCT

A substantial proportion of patients are not eligible for HDT followed by ASCT. This may result from advanced age or comorbidities because they are refractory to second-line treatment or because they express a desire not to undergo the treatment. Patients who are ineligible for HDT followed by ASCT, as described in the bone marrow transplant guidelines, have distinctly lower survival rates (Feugier *et al*, 2005; Thieblemont & Coiffier, 2007). Treatment options comprise conventional chemotherapy, enrolment in phase I or II clinical trials, radiotherapy in localized lesions, rituximab therapy and optimal supportive care (Jabbour *et al*, 2004; Murthy *et al*, 2008).

Regimens for younger patients can be used in fit elderly patients with dose modifications in case of toxicities. Regimens based on the ifosfamide-etopside combination are generally preferred to the cytarabine-cisplatinum combination in the elderly. Rituximab-bendamustine is another popular alternative. The goal is to achieve the best response without unacceptable toxicities and maintain it by spacing the chemotherapy in a maintenance approach. We recommend a quite well-tolerated regimen, such as RGemOx (Mounier *et al*, 2013) rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (RDHAX)/ rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (ROAD) (Lignon *et al*, 2010; Witzig *et al*, 2017).

Monotherapy can be proposed with generally an advantage to pixantrone in the only randomized study (Pettengell *et al*, 2012). A list of selected new agents with some, although limited, activities in DLBCL can found in Table II. Due to their limited activities, most of these agents are not registered for DLBC. The ORR is generally below 50% with a short duration of survival. Nevertheless, they could be a backbone for new combinations. More recently, lenalidomide with rituximab appeared to be quite effective in a phase II study. Inclusion in a prospective study for new drug development is recommended (Zinzani *et al*, 2016).

CAR-T cells: a new revolution?

New therapies are needed for patients with NHLs that are resistant to standard therapies. Indeed, unresponsiveness to standard chemotherapy and relapse after ASCT are indicators of an especially poor prognosis. Therapeutic T cell engineering has recently garnered widespread interest owing to the success of CD19 (Chimeric Antigen Receptor) CAR therapy. CARs are synthetic receptors for antigens that redirect the specificity and reprogram the function of the T cells in which they are genetically introduced. CARs targeting CD19, a cell surface molecule found in most B cell leukaemias and lymphomas, have yielded high remission rates in patients with chemorefractory, relapsed disease, including acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and NHL.

Importantly, anti-CD19 CAR-T cells have impressive activity against chemotherapy-refractory lymphoma, inducing durable complete remissions lasting >2 years in some patients with refractory DLBCL. CAR-T cell therapies are, however, associated with potentially fatal toxicities, including cytokine-release syndrome and neurological toxicities.

In the three reported series on refractory lymphomas, the ORR was impressive, ranging from 59 to 88%, with half of the patients achieving complete remission (Abramson & Chen, 2017; Neelapu *et al*, 2017a; Schuster *et al*, 2017). The duration of the response can exceed 2 years, but it must be evaluated with, at least, a historical control.

Recently, the results of SCHOLAR-1 provided a benchmark for the evaluation of new approaches with CAR-T cells. ZUMA-1 is a prospective, interventional (and the first) multicentre, pivotal trial of an autologous anti-CD19 CAR-T cell therapy, axicabtagene ciloleucel (axi-cel, formerly KTE-C19), in 101 patients with refractory aggressive NHL (Neelapu *et al*, 2017b). A standardized comparison between the ZUMA-1 and SCHOLAR-1 studies has suggested that patients treated with axi-cel experience nearly 10-fold higher odds of CR and a 77% decrease in the risk of death. A randomized study (ZUMA 7) will be conducted to confirm these data, providing a strong rationale for future development in this difficult-to-treat lymphoma.

Considering all of the new drugs available for the treatment of DLBCL lymphoma, we must recognize that none can provide such a response rate with a long duration. However, toxicities and cost pose serious concerns for the development of external specialized centres.

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Competing interests

The authors have no competing interests.

References

Abramson, J.S. & Chen, Y.B. (2017) More on anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. *The New England Journal of Medicine*, **377**, 2102.

Arber, D.A. & George, T.I. (2005) Bone marrow biopsy involvement by non-Hodgkin's lymphoma: frequency of lymphoma types, patterns, blood involvement, and discordance with other sites in 450 specimens. *The American Journal of Surgical Pathology*, **29**, 1549–1557.

Brudno, J., Tadmor, T., Pittaluga, S., Nicolae, A., Polliack, A. & Dunleavy, K. (2016) Discordant bone marrow involvement in non-Hodgkin lymphoma. *Blood*, **127**, 965–970.

Chen, Y.B., Lane, A.A., Logan, B., Zhu, X., Akpek, G., Aljurf, M., Artz, A., Bredeson, C.N., Cooke, K.R., Ho, V.T., Lazarus, H.M., Olsson, R., Saber, W., McCarthy, P. & Pasquini, M.C. (2015a) Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **21**, 1046–1053.

Chen, Y.B., Li, S., Fisher, D.C., Driscoll, J., Del Rio, C., Abramson, J., Armand, P., Barnes, J., Brown, J., Cutler, C., El-Jawahri, A., Ho, V.T., Hochberg, E., McAfee, S., Takvorian, R., Spitzer, T.R., Antin, J.H., Soiffer, R. & Jacobsen, E. (2015b) Phase II trial of tandem high-dose chemotherapy with autologous stem cell transplantation followed by reduced-intensity allogeneic stem cell transplantation for patients with high-risk lymphoma. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **21**, 1583–1588.

Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stroobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V. (2007) International harmonization project on L: revised response criteria for malignant lymphoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **25**, 579–586.

Coiffier, B., Lepage, E., Briere, J., Herbrecht, R., Tilly, H., Bouabdallah, R., Morel, P., Van Den Neste, E., Salles, G., Gaulard, P., Reyes, F., Lederlin, P. & Gisselbrecht, C. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *The New England Journal of Medicine*, **346**, 235–242.

Coiffier, B., Thieblemont, C., Den, Van, Neste, E., Lepeu, G., Plantier, I., Castaigne, S., Lefort, S., Marit, G., Macro, M., Sebban, C., Belhadj, K., Bordessoule, D., Ferme, C. & Tilly, H. (2010) Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*, **116**, 2040–2045.

Crump, M., Kuruvilla, J., Couban, S., MacDonald, D.A., Kukreti, V., Kouroukis, C.T., Rubinger, M., Buckstein, R., Imrie, K.R., Federico, M., Di Renzo, N., Howson-Jan, K., Baetz, T., Kaizer, L., Voralia, M., Olney, H.J., Turner, A.R., Sussman, J., Hay, A.E., Djurfeldt, M.S., Meyer, R.M., Chen, B.E. & Shepherd, L.E. (2014) Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **32**, 3490–3496.

Crump, M., Neelapu, S.S., Farooq, U., Van Den Neste, E., Kuruvilla, J., Westin, J., Link, B.K., Hay, A., Cerhan, J.R., Zhu, L., Boussetta, S., Feng, L., Maurer, M.J., Navale, L., Wiezorek, J., Go, W.Y. & Gisselbrecht, C. (2017) Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*, **130**, 1800–1808.

Cuccuini, W., Briere, J., Mounier, N., Voelker, H.U., Rosenwald, A., Sundstrom, C., Cogliatti, S., Hirchaud, E., Ysebaert, L., Bron, D., Soulier, J., Gaulard, P., Houlgatte, R., Gisselbrecht, C. & Thieblemont, C. (2012) MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. *Blood*, **119**, 4619–4624.

Dunleavy, K., Pittaluga, S., Czuczman, M.S., Dave, S.S., Wright, G., Grant, N., Shovlin, M., Jaffe, E.S., Janik, J.E., Staudt, L.M. & Wilson, W.H. (2009) Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. *Blood*, **113**, 6069–6076.

Feugier, P., Van Hoof, A., Sebban, C., Solal-Celigny, P., Bouabdallah, R., Ferme, C., Christian, B., Lepage, E., Tilly, H., Morschhauser, F., Gaulard, P., Salles, G., Bosly, A., Gisselbrecht, C., Reyes, F. & Coiffier, B. (2005) Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **23**, 4117–4126.

Filmont, J.E., Gisselbrecht, C., Cuenca, X., Deville, L., Ertault, M., Brice, P., De Kerviler, E., Briere, J., Larghero, J., Moretti, J.L. & Mounier, N. (2007) The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer*, **110**, 1361–1369.

Flinn, I.W., Bartlett, N.L., Blum, K.A., Ardeshna, K.M., LaCasce, A.S., Flowers, C.R., Shustov, A.R., Thress, K.S., Mitchell, P., Zheng, F., Skolnik, J.M. & Friedberg, J.W. (2016) A phase II trial to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). *European Journal of Cancer*, **54**, 11–17.

Friedberg, J.W., Sharman, J., Sweetenham, J., Johnston, P.B., Vose, J.M., Lacasce, A., Schaefer-Cutillo, J., De Vos, S., Sinha, R., Leonard, J.P., Cripe, L.D., Gregory, S.A., Sterba, M.P., Lowe, A.M., Levy, R. & Shipp, M.A. (2010) Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood*, **115**, 2578–2585.

Gisselbrecht, C. (2013) Ofatumumab in diffuse large B cell lymphoma? *Blood*, **122**, 469–470.

Gisselbrecht, C., Vose, J., Nademanee, A., Gianni, A.M. & Nagler, A. (2009) Radioimmunotherapy for stem cell transplantation in non-Hodgkin's lymphoma: in pursuit of a complete response. *The Oncologist*, **14** (Suppl. 2), 41–51.

Gisselbrecht, C., Glass, B., Mounier, N., Singh Gill, D., Linch, D.C., Trneny, M., Bosly, A., Ketterer, N., Shpilberg, O., Hagberg, H., Ma, D., Briere, J., Moskowitz, C.H. & Schmitz, N. (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **28**, 4184–4190.

Gisselbrecht, C., Schmitz, N., Mounier, N., Singh Gill, D., Linch, D.C., Trneny, M., Bosly, A., Milpied, N.J., Radford, J., Ketterer, N., Shpilberg, O., Duhrsen, U., Hagberg, H., Ma, D.D., Viardot, A., Lowenthal, R., Briere, J., Salles, G., Moskowitz, C.H. & Glass, B. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20 (+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **30**, 4462–4469.

Hamadani, M., Hari, P.N., Zhang, Y., Carreras, J., Akpek, G., Aljurf, M.D., Ayala, E., Bachanova, V., Chen, A.I., Chen, Y.B., Costa, L.J., Fenske, T.S., Freytes, C.O., Ganguly, S., Hertzberg, M.S., Holmberg, L.A., Inwards, D.J., Kamble, R.T., Kanfer, E.J., Lazarus, H.M., Marks, D.I., Nishihori, T., Olsson, R., Reddy, N.M., Rizzieri, D.A., Savani, B.N., Solh, M., Vose, J.M., Wirk, B., Maloney, D.G., Smith, S.M., Montoto, S., Saber, W., Alpdogan, O., Cashen, A., Dandoy, C., Finke, R., Gale, R., Gibson, J., Hsu, J.W., Janakiraman, N., Laughlin, M.J., Lill, M., Cairo, M.S., Munker, R., Rowlings, P.A., Schouten, H.C., Shea, T.C., Stiff, P.J. & Waller, E.K. (2014) Early failure of frontline rituximab-containing chemoimmunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **20**, 1729–1736.

Hans, C.P., Weisenburger, D.D., Greiner, T.C., Gascoyne, R.D., Delabie, J., Ott, G., Muller-Hermelink, H.K., Campo, E., Braziel, R.M., Jaffe, E.S., Pan, Z., Farinha, P., Smith, L.M., Falini, B., Banham, A.H., Rosenwald, A., Staudt, L.M., Connors, J.M., Armitage, J.O. & Chan, W.C. (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*, **103**, 275–282.

Hernandez-Ilizaliturri, F.J., Deeb, G., Zinzani, P.L., Pileri, S.A., Malik, F., Macon, W.R., Goy, A., Witzig, T.E. & Czuczman, M.S. (2011) Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer*, **117**, 5058–5066.

Herrera, A.F., Rodig, S.J., Song, J.Y., Kim, Y., Griffin, G.K., Yang, D., Nikolaenko, L., Mei, M., Bedell, V., Dal Cin, P., Pak, C., Alyea, E.P., Budde, L.E., Chen, R., Chen, Y.B., Chan, W.C., Cutler, C.S., Ho, V.T., Koreth, J., Krishnan, A., Murata-Collins, J.L., Nikiforow, S., Palmer, J., Pihan, G.A., Pillai, R., Popplewell, L., Rosen, S.T., Siddiqi, T., Sohani, A.R., Zain, J., Kwak, L.W., Weisenburger, D.D., Weinstock, D.M., Soiffer, R.J., Antin, J.H., Forman, S.J., Nademanee, A.P. & Armand, P. (2018) Outcomes after allogeneic stem cell transplantation in patients with double-hit and double-expressor lymphoma. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, **24**, 514–520.

Hoppe, B.S., Moskowitz, C.H., Zhang, Z., Maragulia, J.C., Rice, R.D., Reiner, A.S., Hamlin, P.A., Zelenetz, A.D. & Yahalom, J. (2009) The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. *Bone Marrow Transplantation*, **43**, 941–948.

van Imhoff, G.W., McMillan, A., Matasar, M.J., Radford, J., Ardeshna, K.M., Kuliczkowski, K., Kim, W., Hong, X., Goerloev, J.S., Davies, A., Barrigon, M.D.C., Ogura, M., Leppa, S., Fennessy, M., Liao, Q., van der Holt, B., Lisby, S. & Hagenbeek, A. (2017) Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **35**, 544–551.

Italiano, A., Soria, J.C., Toulmonde, M., Michot, J.M., Lucchesi, C., Varga, A., Coindre, J.M., Blakemore, S.J., Clawson, A., Suttle, B., McDonald, A.A., Woodruff, M., Ribich, S., Hedrick, E., Keilhack, H., Thomson, B., Owa, T., Copeland, R.A., Ho, P.T.C. & Ribrag, V. (2018) Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *The Lancet Oncology*, **19**, 649–659. pii: S1470-2045(18)30145-1. https://doi.org/10.1016/s1470-2045(18)30145-1

Jabbour, E., Chalhoub, B., Suzan, F., Aloulou, S., Cainap, C., Toumi, N., Ferme, C., Carde, P. & Ribrag, V. (2004) Outcome of elderly patients with aggressive Non-Hodgkin's lymphoma refractory to or relapsing after first-line CHOP or CHOP-like chemotherapy: a low probability of cure. *Leukemia & Lymphoma*, **45**, 1391–1394.

Jantunen, E., Canals, C., Rambaldi, A., Ossenkoppele, G., Allione, B., Blaise, D., Conde, E., Tilly, H., Cook, G., Clark, F., Gallamini, A., Haynes, A., Mounier, N., Dreger, P., Pfreundschuh, M., Sureda, A. & Party, E.L.W. (2008) Autologous stem cell transplantation in elderly patients (> or =60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry. *Haematologica*, **93**, 1837–1842.

Jurczak, W., Zinzani, P.L., Gaidano, G., Goy, A., Provencio, M., Nagy, Z., Robak, T., Maddocks, K., Buske, C., Ambarkhane, S., Winderlich, M., Dirnberger-Hertweck, M., Korolkiewicz, R. & Blum, K.A. (2018) Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Annals of Oncology*. https://doi.org/10.1093/annonc/mdy056

van Kampen, R.J., Canals, C., Schouten, H.C., Nagler, A., Thomson, K.J., Vernant, J.P., Buzyn, A., Boogaerts, M.A., Luan, J.J., Maury, S., Milpied, N.J., Jouet, J.P., Ossenkoppele, G.J. & Sureda, A. (2011) 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. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **29**, 1342–1348.

Kansara, R., Connors, J.M., Savage, K.J., Gerrie, A.S., Scott, D.W., Slack, G.W., Gascoyne, R.D., Sehn, L.H. & Villa, D. (2016) Maintenance rituximab following induction R-CHOP chemotherapy in patients with composite or discordant, indolent and aggressive, B-cell non-Hodgkin lymphomas. *Haematologica*, **101**, e411–e414.

de Kerviler, E., Guermazi, A., Zagdanski, A.M., Meignin, V., Gossot, D., Oksenhendler, E., Mariette, X., Brice, P. & Frija, J. (2000) Image-guided core-needle biopsy in patients with suspected or recurrent lymphomas. *Cancer*, **89**, 647–652.

de Kerviler, E., Benet, C., Briere, J. & de Bazelaire, C. (2012) Image-guided needle biopsy for diagnosis and molecular biology in lymphomas. *Best Practice & Research Clinical Haematology*, **25**, 29–39.

Kuruvilla, J., MacDonald, D.A., Kouroukis, C.T., Cheung, M., Olney, H.J., Turner, A.R., Anglin, P., Seftel, M., Ismail, W.S., Luminari, S., Couban, S., Baetz, T., Meyer, R.M., Hay, A.E., Shepherd, L., Djurfeldt, M.S., Alamoudi, S., Chen, B.E. & Crump, M. (2015) Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. *Blood*, **126**, 733–738.

Lesokhin, A.M., Ansell, S.M., Armand, P., Scott, E.C., Halwani, A., Gutierrez, M., Millenson, M.M., Cohen, A.D., Schuster, S.J., Lebovic, D., Dhodapkar, M., Avigan, D., Chapuy, B., Ligon, A.H., Freeman, G.J., Rodig, S.J., Cattry, D., Zhu, L., Grosso, J.F., Bradley Garelik, M.B., Shipp, M.A., Borrello, I. & Timmerman, J. (2016) Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **34**, 2698–2704.

Lignon, J., Sibon, D., Madelaine, I., Brice, P., Franchi, P., Briere, J., Mounier, N., Gisselbrecht, C., Faure, P. & Thieblemont, C. (2010) Rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX) is an effective and safe salvage regimen in relapsed/refractory B-cell non-Hodgkin lymphoma. *Clinical Lymphoma, Myeloma & Leukemia*, **10**, 262–269.

Martin, A., Conde, E., Arnan, M., Canales, M.A., Deben, G., Sancho, J.M., Andreu, R., Salar, A., Garcia-Sanchez, P., Vazquez, L., Nistal, S., Requena, M.J., Donato, E.M., Gonzalez, J.A., Leon, A., Ruiz, C., Grande, C., Gonzalez-Barca, E. & Caballero, M.D.; Grupo Espanol de Linfomas/Trasplante Autologo de Medula O. (2008) 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*, **93**, 1829–1836.

Melani, C., Major, A., Schowinsky, J., Roschewski, M., Pittaluga, S., Jaffe, E.S., Pack, S.D., Abdullaev, Z., Ahlman, M.A., Kwak, J.J., Morgan, R., Rabinovitch, R., Pan, Z., Haverkos, B.M., Gutman, J.A., Pollyea, D.A., Smith, C.A., Wilson, W.H. & Kamdar, M. (2017) PD-1 blockade in mediastinal gray-zone lymphoma. *The New England Journal of Medicine*, **377**, 89–91.

Morschhauser, F.A., Cartron, G., Thieblemont, C., Solal-Celigny, P., Haioun, C., Bouabdallah, R., Feugier, P., Bouabdallah, K., Asikanius, E., Lei, G., Wenger, M., Wassner-Fritsch, E. & Salles, G.A. (2013) Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **31**, 2912–2919.

Mounier, N., El, Gnaoui T., Tilly, H., Canioni, D., Sebban, C., Casasnovas, R.O., Delarue, R., Sonet, A., Beaussart, P., Petrella, T., Castaigne, S., Bologna, S., Salles, G., Rahmouni, A., Gaulard, P. & Haioun, C. (2013) Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study association trial. *Haematologica*, **98**, 1726–1731.

Murthy, V., Thomas, K., Foo, K., Cunningham, D., Johnson, B., Norman, A. & Horwich, A. (2008) Efficacy of palliative low-dose involved-field radiation therapy in advanced lymphoma: a phase II study. *Clinical Lymphoma & Myeloma*, **8**, 241–245.

Neelapu, S.S., Locke, F.L., Bartlett, N.L., Lekakis, L.J., Miklos, D.B., Jacobson, C.A., Braunschweig, I., Oluwole, O.O., Siddiqi, T., Lin, Y., Timmerman, J.M., Stiff, P.J., Friedberg, J.W., Flinn, I.W., Goy, A., Hill, B.T., Smith, M.R., Deol, A., Farooq, U., McSweeney, P., Munoz, J., Avivi, I., Castro, J.E., Westin, J.R., Chavez, J.C., Ghobadi, A., Komanduri, K.V., Levy, R., Jacobsen, E.D., Witzig, T.E., Reagan, P., Bot, A., Rossi, J., Navale, L., Jiang, Y., Aycock, J., Elias, M., Chang, D., Wiezorek, J. & Go, W.Y. (2017a) Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *The New England Journal of Medicine*, **377**, 2531–2544.

Neelapu, S., Locke, F., Bartlett, N., Lekakis, L., Reagan, P., Miklos, D., Jacobson, C., Braunschweig, I., Oluwole, O., Siddiqi, T., Lin, Y., Crump, M., Kuruvilla, J., Van Den Neste, E., Farooq, U., Navale, L., Go, W., Wiezorek, J. & Gisselbrecht, A.C. (2017b) A comparison of one year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). *Blood*, **130**, Abstract 579.

Oki, Y., Kelly, K.R., Flinn, I., Patel, M.R., Gharavi, R., Ma, A., Parker, J., Hafeez, A., Tuck, D. & Younes, A. (2017) CUDC-907 in relapsed/refractory diffuse large B-cell lymphoma, including patients with MYC-alterations: results from an expanded phase I trial. *Haematologica*, **102**, 1923–1930.

Palanca-Wessels, M.C., Czuczman, M., Salles, G., Assouline, S., Sehn, L.H., Flinn, I., Patel, M.R., Sangha, R., Hagenbeek, A., Advani, R., Tilly, H., Casasnovas, O., Press, O.W., Yalamanchili, S., Kahn, R., Dere, R.C., Lu, D., Jones, S., Jones, C., Chu, Y.W. & Morschhauser, F. (2015) Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. *The Lancet Oncology*, **16**, 704–715.

Pettengell, R., Coiffier, B., Narayanan, G., de Mendoza, F.H., Digumarti, R., Gomez, H., Zinzani, P.L., Schiller, G., Rizzieri, D., Boland, G., Cernohous, P., Wang, L., Kuepfer, C., Gorbatchevsky, I. & Singer, J.W. (2012) Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *The Lancet Oncology*, **13**, 696–706.

Philip, T., Guglielmi, C., Hagenbeek, A., Somers, R., Van der Lelie, H., Bron, D., Sonneveld, P., Gisselbrecht, C., Cahn, J.Y., Harousseau, J.L., Coiffier, B., Biron, P., Mandelli, P. & Chauvin, F. (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *The New England Journal of Medicine*, **333**, 1540–1545.

Reddy, A., Zhang, J., Davis, N.S., Moffitt, A.B., Love, C.L., Waldrop, A., Leppa, S., Pasanen, A., Meriranta, L., Karjalainen-Lindsberg, M.L., Norgaard, P., Pedersen, M., Gang, A.O., Hogdall, E., Heavican, T.B., Lone, W., Iqbal, J., Qin, Q., Li, G., Kim, S.Y., Healy, J., Richards, K.L., Fedoriw, Y., Bernal-Mizrachi, L., Koff, J.L., Staton, A.D., Flowers, C.R., Paltiel, O., Goldschmidt, N., Calaminici, M., Clear, A., Gribben, J., Nguyen, E., Czader, M.B., Ondrejka, S.L., Collie, A., Hsi, E.D., Tse, E., Au-Yeung, R.K.H., Kwong, Y.L., Srivastava, G., Choi, W.W.L., Evens, A.M., Pilichowska, M., Sengar, M., Reddy, N., Li, S., Chadburn, A., Gordon, L.I., Jaffe, E.S., Levy, S., Rempel, R., Tzeng, T., Happ, L.E., Dave, T., Rajagopalan, D., Datta, J., Dunson, D.B. & Dave, S.S. (2017) Genetic and functional drivers of diffuse large B cell lymphoma. *Cell*, **171**, e15.

Sauter, C.S., Matasar, M.J., Meikle, J., Schoder, H., Ulaner, G.A., Migliacci, J.C., Hilden, P., Devlin, S.M., Zelenetz, A.D. & Moskowitz, C.H. (2015) Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma. *Blood*, **125**, 2579–2581.

Sauter, C.S., Matasar, M.J., Schoder, H., Devlin, S.M., Drullinsky, P., Gerecitano, J., Kumar, A., Noy, A., Palomba, M.L., Portlock, C.S., Straus, D.J., Zelenetz, A.D., McCall, S.J., Miller, S.T., Courtien, A.I., Younes, A. & Moskowitz, C.H. (2018) A phase I study of ibrutinib in combination with R-ICE in patients with relapsed or primary refractory DLBCL. *Blood*, **131**, 1805–1808.

Schuster, S.J., Svoboda, J., Chong, E.A., Nasta, S.D., Mato, A.R., Anak, O., Brogdon, J.L., Pruteanu-Malinici, I., Bhoj, V., Landsburg, D., Wasik, M., Levine, B.L., Lacey, S.F., Melenhorst, J.J., Porter, D.L. & June, C.H. (2017) Chimeric antigen receptor T cells in refractory B-cell lymphomas. *The New England Journal of Medicine*, **377**, 2545–2554.

Sehn, L.H. & Gascoyne, R.D. (2015) Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood*, **125**, 22–32.

Sellner, L., Boumendil, A., Finel, H., Choquet, S., de Rosa, G., Falzetti, F., Scime, R., Kobbe, G., Ferrara, F., Delmer, A., Sayer, H., Amorim, S., Bouabdallah, R., Finke, J., Salles, G., Yakoub-Agha, I., Faber, E., Nicolas-Virelizier, E., Facchini, L., Vallisa, D., Zuffa, E., Sureda, A., Dreger, P. & Party, E.L.W. (2016) Thiotepa-based high-dose therapy for autologous stem cell transplantation in lymphoma: a retrospective study from the EBMT. *Bone Marrow Transplantation*, **51**, 212–218.

Smith, S.M., van Besien, K., Karrison, T., Dancey, J., McLaughlin, P., Younes, A., Smith, S., Stiff, P., Lester, E., Modi, S., Doyle, L.A., Vokes, E.E. & Pro, B. (2010) Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: the University of Chicago phase II consortium. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **28**, 4740–4746.

Sorror, M.L., Maris, M.B., Storb, R., Baron, F., Sandmaier, B.M., Maloney, D.G. & Storer, B. (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*, **106**, 2912–2919.

Soussain, C., Choquet, S., Fourme, E., Delgadillo, D., Bouabdallah, K., Ghesquieres, H., Damaj, G., Dupriez, B., Vargaftig, J., Gonzalez, A., Houillier, C., Taillandier, L., Hoang-Xuan, K. & Leblond, V. (2012) Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. *Haematologica*, **97**, 1751–1756.

Sun, L., Li, S., El-Jawahri, A., Armand, P., Dey, B.R., Fisher, D.C., Jacobsen, E.D., Jacobson, C.A., LaCasce, A.S., McAfee, S.L., Spitzer, T.R., Chen, Y.B. & DeFilipp, Z. (2018) Autologous stem cell transplantation in elderly lymphoma patients in their 70s: outcomes and analysis. *The Oncologist*, **23**, 624–630.

Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G.A., Zelenetz, A.D. & Jaffe, E.S. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, **127**, 2375–2390.

Terasawa, T., Dahabreh, I.J. & Nihashi, T. (2010) Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. *The Oncologist*, **15**, 750–759.

Thieblemont, C. & Coiffier, B. (2007) Lymphoma in older patients. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **25**, 1916–1923.

Thieblemont, C., Briere, J., Mounier, N., Voelker, H.U., Cuccuini, W., Hirchaud, E., Rosenwald, A., Jack, A., Sundstrom, C., Cogliatti, S., Trougouboff, P., Boudova, L., Ysebaert, L., Soulier, J., Chevalier, C., Bron, D., Schmitz, N., Gaulard, P., Houlgatte, R. & Gisselbrecht, C. (2011) The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **29**, 4079–4087.

Van Den Neste, E., Schmitz, N., Mounier, N., Gill, D., Linch, D., Trneny, M., Milpied, N., Radford, J., Ketterer, N., Shpilberg, O., Duhrsen, U., Ma, D., Briere, J., Thieblemont, C., Salles, G., Moskowitz, C.H., Glass, B. & Gisselbrecht, C. (2016) Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplantation*, **51**, 51–57.

Vellenga, E., van Putten, W.L., van't Veer, M.B., Zijlstra, J.M., Fibbe, W.E., van Oers, M.H., Verdonck, L.F., Wijermans, P.W., van Imhoff, G.W., Lugtenburg, P.J. & Huijgens, P.C. (2008) Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. *Blood*, **111**, 537–543.

Viardot, A., Goebeler, M.E., Hess, G., Neumann, S., Pfreundschuh, M., Adrian, N., Zettl, F., Libicher, M., Sayehli, C., Stieglmaier, J., Zhang, A., Nagorsen, D. & Bargou, R.C. (2016) Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood*, **127**, 1410–1416.

Vose, J.M., Carter, S., Burns, L.J., Ayala, E., Press, O.W., Moskowitz, C.H., Stadtmauer, E.A., Mineshi, S., Ambinder, R., Fenske, T., Horowitz, M., Fisher, R. & Tomblyn, M. (2013) Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **31**, 1662–1668.

Weidmann, E., Kim, S.Z., Rost, A., Schuppert, H., Seipelt, G., Hoelzer, D. & Mitrou, P.S. (2002) Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, **13**, 1285–1289.

Wilson, W.H., Young, R.M., Schmitz, R., Yang, Y., Pittaluga, S., Wright, G., Lih, C.J., Williams, P.M., Shaffer, A.L., Gerecitano, J., de Vos, S., Goy, A., Kenkre, V.P., Barr, P.M., Blum, K.A., Shustov, A., Advani, R., Fowler, N.H., Vose, J.M., Elstrom, R.L., Habermann, T.M., Barrientos, J.C., McGreivy, J., Fardis, M., Chang, B.Y., Clow, F., Munneke, B., Moussa, D., Beaupre, D.M. & Staudt, L.M. (2015) Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nature Medicine*, **21**, 922–926.

Witzig, T.E., Reeder, C.B., LaPlant, B.R., Gupta, M., Johnston, P.B., Micallef, I.N., Porrata, L.F., Ansell, S.M., Colgan, J.P., Jacobsen, E.D., Ghobrial, I.M. & Habermann, T.M. (2011) A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia*, **25**, 341–347.

Witzig, T.E., Johnston, P.B., LaPlant, B.R., Kurtin, P.J., Pederson, L.D., Moore, D.F. Jr, Nabbout, N.H., Nikcevich, D.A., Rowland, K.M. & Grothey, A. (2017) Long-term follow-up of chemoimmunotherapy with rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (ROAD) in patients with relapsed CD20+ B-cell non-Hodgkin lymphoma: results of a study of the Mayo Clinic Cancer Center Research Consortium (MCCRC) MC0485 now known as academic and community cancer research united (ACCRU). *American Journal of Hematology*, **92**, 1004–1010.

Zinzani, P.L., Rigacci, L., Cox, M.C., Devizzi, L., Fabbri, A., Zaccaria, A., Zaja, F., Di Rocco, A., Rossi, G., Storti, S., Fattori, P.P., Argnani, L., Tura, S. & Vitolo, U. (2015) Lenalidomide monotherapy in heavily pretreated patients with non-Hodgkin lymphoma: an Italian observational multicenter retrospective study in daily clinical practice. *Leukemia & Lymphoma*, **56**, 1671–1676.

Zinzani, P.L., Pellegrini, C., Argnani, L. & Broccoli, A. (2016) Prolonged disease-free survival in elderly relapsed diffuse large B-cell lymphoma patients treated with lenalidomide plus rituximab. *Haematologica*, **101**, e385–e386.

