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

Christian Gisselbrecht1 and Eric Van Den Neste2
1Hôpital Saint Louis, Paris, France and 2Cliniques universitaires UCL Saint-Luc, Brussels, Belgium

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/refractory 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 immuno chemotherapy. 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).
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 (Cucuini 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...
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 ($P = 0.08$). If the PFS for the EFR cohort was inferior, it was only apparent during the initial part of the curve, post-ASCT (<9 months, $P < 0.001$); 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 ($P < 0.001$). The authors concluded that ASCT provides durable disease control, regardless of the

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.

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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 (thiopeta TT replacing carmustine) implemented by the European

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**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.
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-Bizaliturri et al (2011) |
| Bortezomib + chemotherapy | NF-kB       | 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               | P13Kδ + 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 DLBCL, 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 allogeneic 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 ASC or treated with a tandem approach of ASC 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, enrollment 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-etoposide 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 (Pettenegel 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 chemoresistant, 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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