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Management of relapsed/refractory DLBCL

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ABSTRACT

Diffuse large B cell lymphoma represents the most common type of non-Hodgkin lymphoma. Although the curability rate is high, around 40% of patients will relapse or exhibit refractory disease. To obtain long-term disease-free survival after relapse, an intensive salvage regimen followed by autologous steam cell transplant remains the standard of care. However, more than 60% of patients will be transplant ineligible, presenting a therapeutic challenge. In this setting, there is no definitive standard approach, as management should be individualized according to patient tolerance. Importantly, these transplant ineligible patients are ideal for consideration of novel agents. In this review, we will discuss the incidence, outcome, and management of relapsed and refractory DLBCL, as well as explore some of the novel agents in development.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent types of lymphoid cancer, accounting for 25% of cases of non-Hodgkin lymphoma (NHL) [1]. Although aggressive, it can be cured in 60–70% of patients following first-line immunochemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) [2–4]. Moreover, patients who achieve event-free status at 24 months from diagnosis have a subsequent overall survival (OS) in the range of an age and sex matched general population [5]. Nevertheless, 30%–40% of patients will exhibit refractory disease or relapse after initial response, which will dramatically reduce their life expectancy. These patients continue to present a therapeutic challenge, and moving toward a more tailored personalized approach is an important goal.

In the past 15 years, improved biologic insight has led to a new classification of DLBCL. Gene expression profiling studies have shown that DLBCL can be divided into at least 2 major subtypes, namely germinal center B-cell (GCB) and activated B-cell (ABC), that reflect different cell-of-origin (COO) and oncogenic pathways and are associated with different clinical outcomes [6–8]. In addition, patients with a dual rearrangement of *MYC* and/or *BCL2* and/or *BCL6,* "double-hit" lymphoma, have been recognized to have a poor prognosis and have been reclassified within the World Health Organization (WHO) Classification into a high-grade category [9–12]. More recently, different mutation-based genetic subtypes of DLBCL have been uncovered [13,14]. The appreciation of this biologic heterogeneity will become increasingly important to ensure that targeted therapies are evaluated in patients who are most likely to benefit.

In this review, we will address the incidence, outcome and standard management of relapsed and refractory DLBCL, as well as explore some of the novel agents in development.

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2. Relapse in DLBCL: incidence and timing

The majority of relapses in patients with DLBCL occur within the first 2–3 years following immunochemotherapy [4,15]. Approximately 10–15% of all DLBCL patients treated with R-CHOP will fail therapy within one year from diagnosis (early relapse or refractory DLBCL) and exhibit a very poor prognosis [16–19], making this population the most important unmet medical need. Very late relapses can also occur [15] as reported in a retrospective analysis by Larouche et al. [20] with an incidence of 3% after 5 years.

2.1. Evaluation at time of relapse

Patients who are amenable to curative therapy should undergo full restaging in order to fully assess the status of their disease and to assess prognosis [21]. Rescreening tests for HIV, hepatitis B and C viruses might be necessary. Protein electrophoresis should also be performed looking for immunoglobulin deficiency secondary to first-line therapy, and also hypo-albuminemia. FDG-PET-CT scan must be performed before salvage initiation [22]. A repeat biopsy at time of relapse should strongly be considered to ensure that an alternate histology is not present, as an indolent lymphoma has been reported on repeat biopsy in approximately 17% of cases with late relapses [20]. Furthermore, different patterns of evolution of acquired oncogenic events under chemotherapy selection pressure has been shown [23,24] and with the introduction of targeted agents, understanding the tumor's mutational status may inevitably guide choice of therapy [25].

3. Salvage therapy options for young and fit patients: ASCT remains the goal

When achievable, high dose therapy followed by autologous stem cell transplantation (ASCT) remains the standard of care for relapsed/refractory (RR) patients with DLBCL under the age of 65–70 years without major comorbidities [26]. A non-cross-resistant salvage regimen is used for initial cytoreduction and to assess chemotherapy sensitivity, since proceeding to ASCT in the setting of chemo-refractory disease is generally futile.

3.1. Choice of salvage regimen

Several salvage therapy regimens have been explored prior to ASCT. The main results of prospective studies in patients with relapsed/refractory DLBCL and eligible for transplantation are presented in Table 1. In the randomized phase III CORAL trial including 396 DLBCL patients in first relapse [27], R-DHAP (dexamethasone, cytarabine and cisplatine) and R-ICE (ifosfamide, carboplatine and etoposide) salvage regimens resulted in a similar overall response rate (ORR) of 63%. In this study, more grade 3–4 toxicities, including renal toxicity and a higher platelet transfusion requirement were reported with R-DHAP. Subsequently, in a separate randomized comparison, Crump et al. [28] demonstrated that R-GDP (gemcitabine, dexamethasone and cisplatin) was non-inferior in efficacy compared to R-DHAP, and had a more favorable toxicity profile characterized by less febrile neutropenia, fewer platelet transfusions, lower rate of hospitalization, better quality of life and lower cost. Taken together, this data suggests that the most commonly used salvage regimens, R-ICE, R-DHAP and R-GDP have similar efficacy and choice of therapy may be guided by individual toxicity considerations. To reduce the toxicity associated with cisplatin in DHAP and GDP, in particular the renal toxicity, combinations incorporating carboplatin or oxaliplatin have been evaluated and may be appropriate for select patients [29–32].

3.2. Role of anti-CD20 monoclonal antibodies in salvage therapy

Historical comparisons have suggested a benefit of the addition of rituximab with various salvage regimens, including ICE [33], DHAP [34] and GDP [35]. However, some of the patients included in these series were not previously treated with rituximab, and prior rituximab exposure was identified to be an adverse prognostic factor [27,36,37]. The only randomized trial evaluating this question was the HOVON-44 phase III trial, in which Vellenga et al. [38] reported an ORR of 75% after 2 cycles of R-DHAP versus

Table 1
Prospective studies in patients with relapsed/refractory DLBCL who are eligible for transplantation.

ASCT eligible	Regimen, N	ORR	ASCT rate	PFS/OS
Sieniawski [34]	R-DHAP, 19	63%	68%	2 y PFS 57% 2 y OS 77%
Kewalramani [33]	R-ICE, 36	53%	69%	2 y PFS 54% 2 y OS 67% (ASCT)
Vellenga [38]	DHAP-VIM-DHAP, 112	54%	46%	2y PFS 31%, OS 52%
(80% DLBCL)	R-DHAP-VIM-DHAP, 113	75% (all NHL)	63%	2 y PFS 52%, OS 59%
Gisselbrecht [21]	R-ICE, 202	63.5%	50%	2 y PFS 31%, 2 y OS 47%
	R-DHAP, 194	62.8%	54%	2 y PFS 42%, 2 y OS 51%
Crump [28]	GDP ± R, 310	44%	52.1%	HR 0.99 PFS
	DHAP ± R, 309	45%	49.3%	HR 1.03 OS
Van Imhoff [39]	R-DHAP, 225	42%	33%	2 y PFS 26%, 2 y OS 38%
	Ofa-DHAP, 222	38%	37%	2 y PFS 24%, 2 y OS 41%

54% in the DHAP arm. However, similarly in this trial, the majority of patients were previously rituximab-naïve.

Alternative anti-CD20 monoclonal antibodies have been evaluated in relapsed/refractory DLBCL. In the phase III ORCHARRD trial, 447 patients were randomly assigned to 3 cycles of R-DHAP or ofatumumab-DHAP followed by ASCT for responders. This trial demonstrated no benefit of ofatumumab compared to rituximab in this setting [39]. Obinutuzumab, demonstrated only modest activity as a single agent (ORR 20%) in rituximab pretreated patients [40]. Furthermore, the randomized GOYA study of obinutuzumab-CHOP vs R-CHOP [41] in untreated DLBCL did not show any difference in ORR or PFS between the 2 cohorts. Overall, there is no data to support the use of an alternate anti-CD20 monoclonal antibody in relapsed/refractory DLBCL at this time.

3.3. Stem cell transplantation conditioning regimen

BEAM (carmustine, etoposide, cytarabine, and melphalan) is the most widely used conditioning regimen for relapsed/refractory DLBCL. The addition of rituximab to pre-transplant conditioning may be beneficial [42,43]. However, a randomized phase 2 trial comparing high dose rituximab (1000 mg/m^2) versus standard dose (375 mg/m^2) combined with BEAM in relapsed/refractory NHL demonstrated no improvement in outcome [44]. Several early trials suggested a possible benefit to the use of rituximab following ASCT [43,45]. However, this was not confirmed in 2 large randomized trials which showed no advantage to maintenance rituximab post-ASCT [27,46].

Radiolabeled monoclonal antibodies, ibritumomab tiuxetan [47] and tositumomab [48], have also been evaluated but both failed to confer any survival benefit to R-BEAM conditioning.

All in all, BEAM or R-BEAM, remains the standard conditioning regimen in this setting.

3.3.1. Outcome and prognostic factors

In the CORAL study, that included 396 patients of whom 60% were previously treated with rituximab, the ORR to first-line salvage was 63% for the entire cohort, leading to a 3-year EFS, PFS and OS of 31%, 37% and 49%, respectively [27]. For patients that underwent ASCT, the 3-year PFS was 53%. In this trial, the most important prognostic factors associated with a poor outcome were previous treatment with rituximab, primary refractory disease and high secondary age-adjusted-IPI score. Interestingly, for patients who experienced a relapse more than 1 year after initial induction, prior exposure to rituximab was no longer a prognostic factor. Furthermore, in this series, a *MYC* gene rearrangement and COO were significantly correlated with a worse PFS and OS [49]. Interestingly, patients with GCB DLBCL had a longer 3-year PFS with R-DHAP than with R-ICE (52% versus 31%) [50]. In the HOVON-44 trial, Vellenga et al. [38] reported a 2-year PFS of 53% for relapsed/refractory patients treated with 2 cycles of R-DHAP followed by VIM (etoposide-ifosfamide-methotrexate)-DHAP and ASCT. In the ORCHARRD study, which included only rituximab-pretreated patients and demonstrated no benefit of ofatumumab-DHAP compared with R-DHAP, the 2-year PFS and OS were approximately 25% and 40% for the entire cohort. Recently, Chahoud et al. [47] reported long-term results following an R-BEAM conditioning regimen and ASCT in patients with chemo-sensitive relapsed/refractory DLBCL. The 5-year DFS and OS rates were quite favorable at 62% and 73%, respectively. In this series, COO and timing of relapse were not associated with outcome.

Retrospective analyses evaluating patients with primary refractory DLBCL have shown less favorable outcomes, with 2-year OS rates ranging from 15% to 35% [16–19,36,51]. Indeed, in the international multicohort retrospective SCHOLAR-1 study evaluating the outcome of refractory DLBCL, the ORR to next line of therapy was 26% (CR 7%) and the median OS 6.3 months [18]. ASCT seem to be a reasonable option in primary refractory patients with chemo-sensitive disease following salvage, since 3-year OS rates ranging from 45 to 65% [51–53] have been reported in this population. That being said, patients with primary refractory disease are less likely to respond to salvage therapy (ORR of 46% versus 88% reported in the CORAL study for patients relapsing within 1 year versus longer following induction [21]) and importantly, in a study reported by Hitz et al. [19], only 16% of primary refractory transplant-eligible patients ultimately proceeded to transplant.

In conclusion, patients with primary refractory DLBCL and those with relapsed/refractory disease who are chemotherapy-resistant to salvage therapy represent an important unmet need and are a population of patients in which consideration of alternative targeted strategies is warranted.

3.3.2. Predictive value of PET-CT prior to ASCT

PET-CT following salvage therapy and prior to transplantation has been shown to be prognostic of outcome [54,55]. Patients achieving a Deauville score of 1–3 after salvage chemotherapy experienced superior 3-year PFS and OS rates of 77% and 86%, respectively, compared to patients achieving a Deauville score of 4 (49% and 54%, respectively) ($P < 0.001$) [55]. As well, in the ORCHARRD trial, PET-CT results after the 3 cycles of ofatumumab-DHAP or R-DHAP were highly predictive of PFS and OS. Responding patients with a positive PET-CT had a 2-year PFS and OS of 32% and 43% compared with 70% and 78% in patients with a negative PET scan ($P = 0.001$ and 0.0018, respectively). These results underscore the need for improved salvage therapy prior to transplantation.

4. Outcome and options after failure of salvage therapy for young patients

4.1. Switch to a different salvage regimen?

Overall, only about 40% of relapsed/refractory transplant-eligible patients proceed to ASCT, mainly because of non-response to salvage therapy. The outcome of these non-transplanted patients is poor and data reporting on their management, ranging from

supportive care to allogeneic transplantation, is scarce. Van den Neste et al. [56] reported observational real-life data of the 170 patients included in the CORAL trial that did not proceed to transplant because of treatment failure. The second salvage therapy received was ICE-like chemotherapy (18%), DHAP-like (18%), gemcitabine-containing (14%), Dexa-BEAM (9%), and CHOP-like (8%) with an ORR of 51.7%, 41.4%, 13.6%, 53.3% and 46.2%, respectively. Switching treatment at time of second salvage from R-ICE to DHAP-like or R-DHAP to ICE-like lead to a comparable ORR. Overall, 31.5% of the CORAL failure patients were eventually transplanted with a median OS of 11.1 months compared to 3.3 months for the non-transplanted patients. Importantly, there was no benefit of allogeneic transplantation compared to ASCT. One third of the patients received rituximab as part second salvage, without influence on outcome. Overall, these data suggest that proceeding to a second salvage therapy may be warranted. This observation was in contradiction with a report by Ardeshna [57] claiming that second salvage regimens were not useful in patients who had progressive disease after initial salvage. Regardless, patients who fail an initial salvage therapy, should strongly be considered for clinical trials of novel approaches.

4.2. A role for allogeneic transplantation?

Several studies have reported a potential for curability after allogeneic transplantation for patients with relapsed/refractory DLBCL, with prolonged OS as high as 48% at 4 years [58–60]. However, limitations of allogeneic transplantation include difficulty finding a matched donor and a high rate of non-relapse mortality (NRM) that is frequently higher than relapse-related mortality. Therefore, allogeneic transplantation is usually reserved for select patients who have relapsed after ASCT. To illustrate that point, Robinson et al. [61] reviewed the outcome of 4210 patients with relapsed/refractory DLBCL that underwent an ASCT or allogeneic transplant (N = 230) as their first transplant procedure and showed that the 4-year NRM rate was 7%, 20% and 27% for ASCT, reduced-intensity conditioning (RIC) and myeloablative conditioning (MAC) allogeneic transplant, respectively. The 4-year OS was 60%, 52% and 38% for ASCT, RIC and MAC, respectively. After adjustment for confounding factors, NRM was significantly worse for patients undergoing an allogeneic transplant whilst there was no difference in the relapse incidence. Fenske et al. [62] analyzed the outcome of a selected population of 503 patients relapsing after ASCT who proceeded to allogeneic transplantation. They reported a 3-year NRM, PFS and OS rate of 30%, 31% and 37%, respectively. Importantly, in this study the factors associated with poor outcome included a poor performance status, chemotherapy resistance and MAC allogeneic transplant, supporting the rationale for reserving allogeneic transplantation for a select population of patients. However, in the past 15 years, progress in peri-transplantation supportive care and RIC transplantation has led to a reduction in NRM, but at the price of a higher risk of lymphoma relapse [60,63–65]. Another important recent advance has been the use of haplo-identical related donors which has increased the likelihood of finding a donor for individual patients [66]. In combination with specific graft-versus-host disease (GVHD) prophylaxis this procedure leads to a significantly lower risk of grade 3–4 acute GVHD compared with unrelated donor transplantation and a similar relapse risk, NRM, PFS and OS.

5. Management of transplant-ineligible patients

While some elderly fit patients may proceed to ASCT and exhibit comparable outcomes to younger patients [67,68], the majority will have comorbidities that will preclude intensive therapeutic approaches. However, various multi-agent salvage regimens have been explored in this elderly population. Long-term analysis of the initial front-line R-CHOP versus CHOP study [69] (including patients aged 60–80 years at diagnosis) revealed that relapsing patients were treated with salvage regimens including DHAP, ESHAP or ICE and that only one patient underwent ASCT. The 2-year OS was 26% and 31% for these elderly patients relapsing after R-CHOP and CHOP, respectively. The benefit of rituximab as part of salvage therapy appeared to be limited to those who were treated initially with CHOP alone. However, an analysis of patients relapsing after R-CHOP/CHOP in the RICOVER trial showed that the ORR to salvage was 47% [36] and that the benefit of rituximab retreatment was also seen in patients initially treated with R-CHOP (2-year OS of 33% compared to 22% following salvage with or without rituximab, ($p = 0.034$)).

Few prospective trials have been conducted in elderly patients with relapsed/refractory DLBCL. The combination of R-GEMOX was evaluated in a phase II trial which included 49 patients with relapsed/refractory DLBCL, many of whom were elderly (median age 69 years). After 4 cycles, the ORR was 61% (44% of CR) and 5-year PFS and OS were 13 and 14%, respectively. This combination was well tolerated with grade 3–4 infections occurring in only 22% of patients [70]. In another prospective trial, GDP was found to be more effective than ESHAP with a higher ORR (63% vs 55%) and 3-year OS (21% vs 12%) [71]. In a retrospective study, Arcari et al. evaluated the safety and efficacy of R-bendamustine in 55 relapsed/refractory DLBCL patients. The ORR was 50% and median OS 11 months with a good safety profile [72]. A retrospective analysis of R-DHAOX (replacing cisplatin in DHAP by oxaliplatin) in 91 relapsed/refractory NHL patients, including patients with DLBCL, (median age of 60 years) reported an ORR of 75% and 2-year OS of 75%, with a manageable toxicity profile, even among the elderly population [30]. The R-GEM-P combination (rituximab, gemcitabine, cisplatin and methylprednisone) was also retrospectively assessed in 45 relapsed/refractory DLBCL patients at time of first relapse [73] leading to an 0RR of 61% and 3-year OS of 49%.

Recently, Pixantrone, a novel aza-anthracenedione anthracycline-like drug, showed some efficacy as a single agent compared to other chemotherapeutic agents in heavily pre-treated patients [74] leading to its approval in relapsed/refractory DLBCL by both the FDA and EMA. However, in a UK retrospective analysis including 85 patients, the ORR of 24% was disappointing and the median OS was only 3.4 months [75].

In conclusion, in transplant-ineligible patients with relapsed/refractory DLBCL, no standard approach can be proposed given that management is largely palliative and treatment in this primarily elderly population is limited by toxicities. Selection of combination

regimens or sequential single agents should be individualized according to patient tolerance. This cohort of patients is ideal for consideration of novel agents.

6. Novel approaches

Altogether, more than 70% of patients with relapsed/refractory DLBCL represent an unmet medical need due to being either transplant-ineligible or chemo-refractory. For these cases, new approaches are warranted. Among them, chimeric antigen receptor (CAR)-T cell therapy, a cellular therapy using autologous genetically modified T-cells has shown significant promise and has recently been approved by the FDA for this indication.

6.1. CAR-T

Several anti-CD19 CAR-T cell products have been undergoing evaluation in patients with relapsed/refractory DLBCL with very encouraging results. Based on results from a pivotal phase 2 trial (ZUMA-1) the FDA approved axicabtagene ciloleucel for patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy. In this phase II trial, the ORR in 108 patients with at least 6 months of follow-up was 42%, with a CR rate of 40% [76]. With a median follow-up of 15.4 months, the 18-month PFS and OS were estimated to be 41% and 52%, respectively. Two additional CAR-T cell products, CTL019 and JCAR07 have also been undergoing evaluation in patients with relapsed/refractory DLBCL and early results have shown similar promise [77,78]. A phase 2 trial of CTL019 (28 patients) reported an ORR of 64% (CR rate 43% in DLBCL) and after a median follow-up of 28 months, 86% of responding patients with DLBCL had ongoing benefit, also leading to FDA approval [78]. In the DLBCL cohort from the JCAR07 trial, the ORR and CR rate in patients with at least 6 months of follow-up was 40% (14/35) and 37% (13/35), respectively [77]. Based on differences in trial design and patient selection, comparison of results between CAR-T cell trials is difficult. Reported toxicities have been similar, with cytokine release syndrome and neurologic adverse events being a primary concern and requiring unique management. These recent clinical trials have demonstrated that centralized CAR-T-cell manufacturing is feasible, and may represent an important new therapy for patients with relapsed/refractory DLBCL [79]. However, longer follow-up and further evaluation will be required to fully understand the potential impact of this therapy in this setting and which patients will most likely benefit.

6.2. Novel agents

Many novel targeted agents are undergoing evaluation in patients with relapsed/refractory DLBCL. Lenalidomide is an immunomodulatory agent with pleiotropic anti-tumor activity, with preferential activity in the ABC subtype of DLBCL. In stage 1 of a phase 2/3 trial investigating lenalidomide 25 mg daily versus investigator's choice (IC: single agent gemcitabine, rituximab, etoposide, or oxaliplatin) in 102 patients with relapsed/refractory DLBCL, lenalidomide-treated patients had a higher ORR of 27.5% versus 11.8% in the IC arm and the median PFS was improved (13.6 weeks versus 7.9 weeks ($P = 0.041$). A greater improvement was observed in non-GCB patients (median PFS 15.1 vs. 7.1 weeks; $P = 0.021$) compared with GCB patients (10.1 vs. 9.0 weeks; $P = 0.550$) [80]. Immune check-point blockade with the anti-PD1 monoclonal antibody nivolumab demonstrated only modest activity in relapsed/refractory DLBCL in a phase 1b study, resulting in an ORR of 36% and a median duration of response of 22 weeks [81]. Blinatumomab, a CD3/CD19 bispecific T-cell engaging antibody construct leading to T-cell activation and lymphoma cell lysis has been evaluated in a phase I and II trial [82] with an ORR of 55% in DLBCL treated patients at the recommended phase 2 dose but 43% in the phase II. However, concerning toxicities including neurologic adverse events remained a challenge and further evaluation is required [83]. Polatuzumab vedotin, an anti-CD79b antibody-drug conjugate combined with monomethyl auristatin E (MMAE) has demonstrated promising activity in relapsed/refractory DLBCL both as a single agent (ORR of 56%) [84] and in combination with bendamustine and rituximab (BR) (improved overall survival compared with BR alone) [85]. These results have led to an ongoing randomized phase III trial in the first-line setting (NCT03274492) that will compare R-CHOP versus R-CHP-polatuzumab. The BTK inhibitor, ibrutinib has shown preferential efficacy in the ABC subtype of DLBCL with an ORR of 37% reported in relapsed/refractory patients and a biological rationale that is now well understood [86]. Furthermore, in a phase I study, Sauter et al. reported that the combination of ibrutinib and R-ICE was safe, tolerable and did not interfere with stem cell collection. Among the 20 included patients, the ORR was 90% with a CR rate of 55% [87]. Additional combination studies with R-DHAP/Ox are ongoing (Biblos Trial, NCT02055924). Finally, Davids et al. [88] recently reported the results of a phase I trial of the BCL2 inhibitor venetoclax in 106 patients with relapsed/refractory NHL. The ORR in patients with DLBCL was modest at 18%. A combination trial of venetoclax with ibrutinib is currently ongoing (NCT02987400).

In conclusion, CAR-T cell therapy represents a revolutionary new option for RR DLBCL patients, however, it comes with notable toxicities and economic challenges. Modest responses rates offered by other novel drugs warrant evaluation in combination approaches in attempt to improve efficacy.

7. Conclusion

Patients with relapsed/refractory DLBCL present an ongoing challenge. Rituximab combined with platinum-based salvage chemotherapy followed by ASCT should be considered in transplant-eligible patients, as this does offer some patients a chance of cure. Importantly, ASCT should only be performed in patients with chemo-sensitive disease, as proceeding to transplant in chemo-

refractory patients is generally futile. For transplant-ineligible patients, as well as patients with chemotherapy-refractory disease, treatment is largely palliative. In this population, management should be individualized according to patient tolerance, using multi-agent regimens with favorable toxicity profiles or sequential single agents. This challenging group of patients represents the greatest unmet need in DLBCL and are ideal for consideration of clinical trials with novel agents. Indeed, the recent FDA approval of CAR-T cell therapy may offer a new therapeutic option for select patients with relapsed/refractory DLBCL. Other targeted strategies in development are also showing promise, and numerous trials exploring combinations of agents are underway. Importantly, moving forward, a greater appreciation of the underlying biology and molecular determinants within individual patients will be necessary in order to guide the choice of therapy.

Practice points

1. Relapsed/refractory DLBCL remains a treatment challenge.
2. Autologous stem cell transplantation remains the standard of care in young/fit patients with chemo-sensitive disease and offers the best chance of cure.
3. Management in transplant-ineligible patients or those with chemo-refractory disease is largely palliative and there is no current standard of care.

Research agenda

1. All patients with relapsed/refractory DLBCL should undergo repeat tissue biopsy as improved biological understanding of the heterogeneity of the disease is imperative to developing individualized therapy.
2. All patients with relapsed/refractory DLBCL should be considered for clinical trials of novel agents, as outcomes remain poor and a growing list of targeted agents are under evaluation and showing promise.

Conflicts of interest

L. Sehn: honoraria/consultancy: Amgen, Abbvie, Astra Zeneca, Celgene, Roche/Genentech, Lundbeck, Morphosys, Seattle Genetics, TG Therapeutics, Merck, Janssen, Gilead, Karyopharm.

C. Sarkozy: honoraria/consultancy: Roche/Genentech.

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