Best Practice & Research Clinical Haematology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Management of relapsed/refractory DLBCL

Clémentine Sarkozy[a,b], Laurie H. Sehn[b,*]

[a] Cancer Center of Lyon (CRCL), INSERM U1052 – CNRS UMR5286, Lyon, France
[b] British Columbia Cancer Centre for Lymphoid Cancer and the University of British Columbia, Vancouver, British Columbia, Canada

ARTICLE INFO

Keywords:
Diffuse large B cell lymphoma
Relapse
Refractory
Treatment

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.

* **Corresponding author**. 600 West 10th Avenue Vancouver, BC, V5Z 4E6, Canada.
E-mail address: lsehn@bccancer.bc.ca (L.H. Sehn).

https://doi.org/10.1016/j.beha.2018.07.014
Received 20 July 2018; Accepted 20 July 2018

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%