

Management of relapsed-refractory diffuse large B cell lymphoma

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Abstract

Relapsed-Refractory Diffuse Large B Cell Lymphoma (RR DLBCL), which accounts for approximately one-third of patients with DLBCL, remains a major cause of morbidity and mortality. Managing RR DLBCL continues to be a challenge to the treating hemato-oncologist. Salvage high-dose chemotherapy followed by autologous stem cell transplantation is the standard of care for chemosensitive relapses in DLBCL. Various salvage regimens are available, but the quest for an optimal regimen continues. The addition of rituximab to the salvage regimen has improved the outcome of RR DLBCL. Several pertinent issues regarding the management of RR DLBCL are discussed in this short review.

Key words: Activated B cell, autologous stem cell transplant, diffuse large B cell lymphoma, germinal center B, high dose chemotherapy, relapsed refractory

Introduction

Non-Hodgkin lymphoma (NHL) is the seventh most common malignancy.^[1] Diffuse large B cell lymphomas (DLBCLs) are the commonest subtype of NHL. They constitute about 30 to 40% of adult NHLs.

Diffuse large B cell by definition is a large transformed B cell with nuclear diameter more than twice that of a normal lymphocyte. In the recent 2008 WHO classification, DLBCL is classified under the diagnostic heading of “mature B cell neoplasms.” DLBCL is a distinct group in itself with many subtypes and entities based on morphology, immunophenotypic characteristics, and clinical presentation. DLBCL Not Otherwise Specified (NOS) is the commonest variety.^[2,3] Using gene-expression profiling, cell-of-origin studies suggested that there are at least 3 distinct subtypes of DLBCL: Activated B-cell (ABC), germinal center B-cell (GCB), and primary mediastinal DLBCL. These differ in the postulated stage of cell of origin, gene expression, and response to anthracycline-based chemotherapy. The GCB DLBCL has better response rate than ABC DLBCL.^[4,5]

DLBCL could present *de novo* or as a histologic transformation of other low-grade B cell lymphomas like follicular or chronic lymphocytic leukemia/small lymphocytic lymphoma. The *de novo* DLBCLs have better prognosis than the latter group.^[6] Rituximab with CHOP is

the widely accepted first line regimen for the management of DLBCL.^[7]

Relapsed refractory DLBCL

Approximately 50 to 60% of patients with DLBCL achieve and maintain complete remission after first-line therapy; 30 to 40% relapse and 10% have refractory disease.^[8,9] Relapsed refractory DLBCL (RR-DLBCL) is defined as per criteria proposed by Cheson *et al.* [Table 1].^[10] Patients with RR-DLBCL have a poor outlook. If left untreated, RR-DLBCL has a life expectancy of 3 to 4 months.^[11]

Diagnosis

Refractory disease is diagnosed during response assessment to primary treatment. Relapsed DLBCL can be clinically silent and is often diagnosed on routine follow-up. If clinical features and/or imaging findings suggest relapse, an excision biopsy should always be performed because RR-DLBCL has poor prognosis. Disease should be restaged at relapse with a CT scan of the chest/abdomen/pelvis and a bone marrow biopsy as it has prognostic value.^[12] A PET-CT may further delineate extranodal and/or new site involvement.^[13] Patients with CNS symptoms should be evaluated with CT-head and lumbar puncture for CSF cytology and flow cytometry. The IPI (international prognostic index) should be determined again at relapse.^[12]

Standard treatment

High-dose therapy followed by autologous stem cell transplant (HD-ASCT) is the mainstay of therapy for RR-DLBCL. But, all patients are not fit or eligible for this therapeutic option. The treatment of RR-DLBCL is described under the headings of treatment for patients eligible for HD-ASCT and not eligible for HD-ASCT.

Patients eligible for HD-ASCT

The landmark PARMA trial has established HDT-ASCT as the standard of care for RR-DLBCL. This approach salvages 30 to 40% of patients with DLBCL, who relapse after initial therapy.^[14] Therefore, the initial approach to RR DLBCL management is to determine whether the patient is suitable for HD-ASCT.

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For patients suitable for HD-ASCT, various salvage chemotherapeutic regimens are available. Before the Rituximab era, DHAP, ICE, MIME, and Mini-BEAM were some of the commonly used salvage therapies [Table 2].^[14-17] Refractory DLBCL is also managed with these salvage regimens but has poor outcome.

The overall response rates with MIME^[18] and EPOCH^[19] were 60% and 74%, respectively. The wide range of response rate in these trials is attributed not only to the differential efficacy of various chemotherapeutic drugs, but also to the patient population belonging to different age groups. At our center, we prefer R-DHAP as the HDT because it is cheaper and has fewer infectious complications than other HDTs. Our observation is supported by the good results observed in our subset of patients (unpublished personal observation).

Role of rituximab

Rituximab monotherapy yielded good results in RR DLBCL.^[20] Encouraged with these results, Rituximab was added to almost every salvage regimen available. Addition of Rituximab improved the response rates. This allowed more number of patients to undergo ASCT and improved the progression-free survival (PFS), disease-free survival, and overall survival (OS). The major drawback of these trials in the present scenario is that majority of patients had not been previously exposed to Rituximab. In the relapsed setting, the PFS and OS is better in R naïve patients (R-) than those who have been exposed to R previously (R+), especially for the early relapses (relapse within 12 months).^[21,22] In the current scenario where majority patients have already been exposed to Rituximab, its role in the salvage chemotherapy needs to be reestablished, especially with respect to the emergence of Rituximab resistance, like in follicular lymphoma. Several other chemotherapeutic regimens have also shown increased response after addition of Rituximab to salvage chemotherapy. These responses are seen without any increase in toxicity and without affecting the stem cell collection [Table 3].^[23-30]

Gold standard salvage chemotherapy

An ideal salvage chemotherapeutic regimen should have higher response rates with minimal toxicity and should not have adverse effect on the stem cell harvest. Many options are available as salvage chemotherapy. RDHAP and RICE are the two widely used regimens worldwide. Which one is the best regimen? This issue has been addressed in the recently completed multicenter phase 2 CORAL STUDY, with an initial randomization between R-ICE x 3 vs. R-DHAP x 3 followed by BEAM-ASCT [Table 4]. A second randomization then allocated patients to maintenance treatment with Rituximab vs observation. In the first phase results of the trial, there was no significant difference in the response rate, 3-year EFS, or OS between the 2 salvage regimens.^[22] However, an updated analysis of the CORAL study revealed that patients with GCB DLBCL (but not

Table 1: Response criteria for NHL

Relapsed disease	Progressive disease/ non-responders
Appearance of any new lesion or increase by more than 50% in the size of previously involved sites after achieving remission	More than 50% increase from nadir in the SPD* of any previously identified abnormal node
More than 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD* of more than one node	Appearance of any new lesion during or at the end of therapy

*SPD=Sum of product of diameters, NHL=Non-Hodgkin lymphoma

Table 2: Salvage chemotherapeutic regimens in the pre-rituximab era

Regimen (reference)	n	Response rate (%)	Number transplanted (%)	Event-free survival (%)
DHAP ^[14]	215	58	55 (26)	24 at 3 years
ICE ^[15]	163	66	96 (59)	35 at 3 years
Mini BEAM ^[16]	102	43	38 (37)	22 at 3 years
ESHAP ^[17]	122	645	-	10 DFS at 40 months

DFS=Disease-free survival, DHAP=Dexa, high dose cytarabin, cisplatin, ICE=Ifosfamide, carboplatin, etoposide, BEAM=Carmustine, etoposide, cytarabine, melphalan, ESHAP=Etoposide, solumedrol, high dose cytarabin, cisplatin

non-GCB DLBCL) appeared to benefit from salvage treatment with R-DHAP rather than R-ICE.^[31]

Patients ineligible for HD-ASCT

According to standard bone marrow transplant guidelines, patients with severe concomitant medical or psychiatric illness, active central nervous system involvement, or HIV seropositivity are considered ineligible for ASCT. Other criteria for ineligibility includes a bilirubin level >2 mg/dL, creatinine level >1.5 mg/dL, low cardiac ejection fraction (<50%), and a forced expiratory volume in 1 second <50% and/or carbon monoxide diffusion test <50% of predicted level.^[32] These patients have little chance at prolonged control of disease with a dismal outcome. The treatment option for these patients includes participation in phase 1/2 clinical trials with novel and experimental agents (vide infra in the future trends section). Patients are often offered palliation with radiotherapy^[33] radioimmunoconjugates^[34] or rituximab monotherapy.^[35]

Prognostic factors in relapsed/refractory DLBCL:

- Relapsed vs refractory disease
Relapsed patients have higher OR than refractory patients.^[24]
- Age Adjusted International Prognostic Factors Index
Patients with more risk factors (stage III/IV disease, serum LDH level greater than normal, and Karnofsky performance status less than 80%) perform worse than patients with less risk factors.^[12]
- Rituximab naïve status
Rituximab naïve patients have better response rate.^[21]

Table 3: Salvage chemotherapeutic regimens in the rituximab era

Salvage regimen (reference)	Response rate (%)	Progression-free survival
R-DHAP-VIM-DHAP vs DHAP-VIM-DHAP ^[23]	75 vs 54; OR	52% vs 31%; $P < 0.002$ (2-year post-ASCT)
R-ICE vs ICE ^[24]	53 vs 27; CR	54% vs 43%; $P = 0.25$ (2-year post-ASCT)
R-ESHAP ^[25]	OR 92	At median 17 months, median OS and PFS not reached
RICE vs ICE ^[26]	CR 55 vs 28	-
R-GemOx ^[27]	OR 82 after 4 cycles OR 73 after 8 cycles	-
R-DHAX ^[28] (DLBCL+Follicular Lymphoma)	OR 75, CR 57	2-year probability rates of overall survival and progression-free survival were 75% and 43%, respectively
RGIFOX ^[29] (DLBCL+Mantle+Follicular Lymphoma)	OR 77	Failure-free survival 79.6% at median follow-up of 6 months
High-dose sequential therapy with rituximab ^[30]	-	With R ($n = 303$) and without R ($n = 251$) 5-yr OS: 56%, EFS: 45%

*OR=Overall response rate, #CR=Complete response rate, NR=Not reached, DHAP=Dexa, high dose cytarabin, cisplatin, ICE=Ifosfamide, carboplatin, etoposide, R-ESHAP=Rituximab, etoposide, solumedrol, high dose cytarabin, cisplatin, R-DHAX=Rituximab, Dexamethasone, cytarabin, oxaliplatin, RGIFOX=Rituximab, gemcitabine, ifosfamide, oxaliplatin, EFS=Event free survival, VIM=Etoposide, ifosfamide, methotrexate, R-GemOx=Rituximab, gemcitabine, oxaliplatin, PFS=Progression-free survival, ASCT=Autologous stem cell transplant

Table 4: CORAL study

RICE	RDHAP
$n = 202$	$n = 194$
Response rates 63.5%	Response rates 62.8%

RICE=Rituximab, ifosfamide, carboplatin, etoposide, RDHAP=Rituximab, dexa, high dose cytarabin, cisplatin

- Time to relapse
Relapse within one year is a poor risk factor.^[23,36]

Interestingly, the molecular subtype GCB or ABC have no prognostic value for relapsed/refractory DLBCL.^[37,38]

Relapse after HD-ASCT

The prognosis of patients who relapse after HD-ASCT is extremely poor and the median survival is approximately 3 months.^[39] The optimal management of patients with DLBCL relapsing after HD-ASCT is difficult and no standard treatment has been defined. Palliation,^[40] second ASCT or non-myeloablative allogeneic stem cell transplant (AlloSCT)^[41] are some of the options available for these patients. Second ASCT is rarely feasible.

Can we predict which patients will relapse or prove refractory?

Search for the predictors of relapse or refractory disease in DLBCL is on. The probable candidates in line are IPI at presentation,^[42] CNS status,^[43] immunoblastic histology,^[44] molecular markers such as c-myc,^[45] stromal signatures,^[46] and interval PET scan.^[47] Simple markers like absolute monocyte to absolute lymphocyte ratio at presentation^[48] can also be useful in resource-constrained settings. In future, the treatment of DLBCL will be tailored according to the risk of relapse. Further studies need to validate this approach.

Future trends:

Various efforts have been made to improve the outcome of RR DLBCL.

- Addition of rituximab post ASCT as maintenance/consolidation^[49]
- Addition of other monoclonal antibodies to rituximab^[50]
- Use of radioimmunoconjugates as palliation, as augmentation of HDT, or as part of conditioning regimen^[51]
- Use of novel agents like bortezomib,^[52] enzastaurin,^[53] everolimus,^[54] lenalidomide,^[55] fostamatinib,^[56] etc.

Conclusions

- High-dose chemotherapy followed by ASCT is the ideal treatment for eligible chemosensitive patients with RR DLBCL
- The gold standard regimen for salvage chemotherapy does not exist. Superiority of one regimen (RICE or RDHAP) over other is not established, though some trends may emerge on further maturation of data from the CORAL study
- Salvage regimen should contain Rituximab with platinum-based chemotherapy, as this combination is capable of producing high OR and CR rates
- Various options for palliation are available for patients who cannot be offered HDT followed by ASCT
- Advances are needed to improve the outcomes of RR DLBCL by developing newer drugs for salvage and for optimizing ASCT.

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