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Aggressive lymphoma - Section 2

Relapsed aggressive lymphoma: Can we optimize the therapy

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Take-home messages

- Prognostic factors in relapse/refractory patients with DLBCL have been identified and may help to optimize their management.
- The standard salvage approaches in transplant eligible and non-eligible patients have not markedly improved in recent years.
- New agents, from targeted therapies to immune-based approaches, are currently developed, and it will be important to define priorities in their evaluation

Introduction

The outcome of patients with DLBCL has been markedly improved with the introduction of rituximab but about 40 to 50% of them still experience either disease refractoriness or relapse after having achieved response to first line therapy. The prognosis of patients with refractory disease or early relapses is usually very dismal, while a sizable minority of patients with late disease recurrence may still have a chance to be cured, especially when eligible for autologous transplant. In this context, the development of new therapies is urgently needed, and some promising approaches have been recently explored. In this review, we will discuss new data regarding the characteristics of these relapsed/refractory (R/R) patients and their prognosis. The results and limitations of current treatment options in transplant eligible and non-eligible patients will be discussed, before addressing some of the new options under investigation.

Characteristics and prognosis of R/R DLBCL patients

Logically, the population of patients failing first line treatment is enriched in patients with adverse clinical and biological prognostic features at diagnosis, including older age, advanced Ann Arbor stage, elevated LDH, extranodal disease and poor performance status. Furthermore, the proportion of patients with biological characteristics such as a non-GCB subtype, the presence of double-hit translocations involving *MYC*, or the expression of Myc and Bcl2 proteins also appears to be increased. Previous administration of rituximab during first line therapy is also associated with a worse outcome, as shown in prospective studies evaluating different strategies in both transplant eligible and non-eligible patients,[1,2] although this finding was not reproduced in some retrospective studies.[3] Overall, with the improvement made in the optimal management of patients from diagnosis (rituximab being given to all patients and potential personalized treatment in the near future), R/R DLBCL patients will represent more and more a very difficult to treat population.

This group of R/R patients is still heterogeneous (Table 1). Among the different prognostic criteria identified, delay from initial therapy and International Prognostic Index (IPI) at time of failure remain the major prognostic parameters for those patients before they start any second line therapy.[1] Patients with early failure (occurring within 6 to 12 months after the end of first line therapy) appear to have a similar prognosis to those unable to achieve a response at the end of this treatment, or who experience disease progression during first line treatment, although some data suggest that this latter group has an even worse prognosis. Recently, a group of US investigators defined a "ultra-high risk" group of patients (overall survival at 2 years of 13%) as those having at least one of the 3 following criteria: primary progression, high NCCN-IPI index[4] at time of treatment failure or the presence of a translocation involving *C-MYC*.[5] The unfavorable outcome of patient carrying a *C-MYC* translocation was already reported in the CORAL study.[6] The role of other biological tumor characteristics remains unclear. Some studies did not find outcome differences according to the cell of origin classification of DLBCL,[5-7] but most series were relatively small. Interestingly, in the CORAL study,[8] the outcome of patients with a GCB phenotype (but no those with a non GCB or ABC phenotype) appeared influenced by the regimen used for salvage: GCB

patients having received a high-dose cytarabine and cisplatin combination (R-DHAP) had a better outcome than those having received an ifosfamide/etoposide/carboplatin regimen (R-ICE). One report also indicated that patients with R/R DLBCLs expressing both the Bcl-2 and the Myc protein also had an inferior survival.[9] Interesting findings regarding the clonal evolution of patients after treatment suggest that different clonal evolution patterns may be found uin relapsed DLBLC.[10]

Results and limitation of current salvage regimens

The possibility to deliver a curative treatment in R/R DLBCL patients is greatly influenced by the patient ability to tolerate an efficient salvage therapy followed by a consolidation usually consisting in an autologous stem cell transplant (ASCT). Age and comorbidities are hence major parameters taken into consideration when choosing the second line strategy. The use of various combinations including several components such as cytarabine or gemcitabine, platinum salts, other alkylating agents (ifosfamide) or eventually different anthracyclins (with potentially less cardiotoxicities, i.e. mitoxantrone, pixantrone) were assessed in many small series, but only few trials have evaluated their respective benefits.

For transplant eligible patients, R-DHAP, R-ICE or R-GDP regimens are all able to bring about half of the patients to an optimal response before ASCT.[1,11] It has been suggested that some more intense (and complex) salvage regimens before ASCT might eventually improve outcome.[12] It is important to try to develop newer regimens with an increased efficacy, and evaluation of new targeted molecules combined with standard salvage regimens is underway. There has been no substantial progress in the ASCT conditioning regimen in recent years, even with use of radio-immunotherapy,[13] and rituximab maintenance was not able to diminish the risk of relapse after ASCT in DLBCL.[14] Of note, some other lessons may have been retrieved from the CORAL study. While many physicians will advocate that failing a first salvage regimen identify truly refractory patients that are incurable, Van den Nest and colleagues reported that some patients might achieved a new CR with another alternate regimen, and if offered ASCT, may be cured, especially if they had a low IPI index at relapse.[15] A quite small group of a patients relapsing more than 12 months after ASCT might be eligible for a second attempt of effective treatment with allogeneic stem cell transplant (allo-SCT).[16] Finally, recent reports regarding the respective role of auto-SCT and allo-SCT in relapsing DLBCL did not indicate that an allogeneic approach would be better than ASCT.[17] Allo-SCT indications remain then limited, probably for patients who failed after ASCT or for highly selected patients.

For transplant ineligible patients, many regimens were used over the last 20 years, with a median progression free survival unfortunately not exceeding 6 months and a minority of patients (10-15%) still alive after 5 years.[5] Recently, bendamustine was reported to have some efficacy in small series,[18] but discordant data were reported and comparative studies are lacking. For transplant ineligible patients, although commonly used by many physicians, the role of rituximab in the second line remains undetermined, especially in those with refractory disease or early failure.

Future directions in DLBCL patients with R/R disease

Many new targeted agents are currently being developed in lymphoma.[19,20] Some of them, such as antibody drug conjuga-

Table 1. Prognostic factors in patients with R/R DLBCL and consequences.

In all series	
- Age	eligibility for ASCT (also depends on comorbidities)
- IPI or NCCN-IPI at relapse	poor outcome for higher scores, consider clinical trials +++
- Delay between first line and disease progression	although variably defined, early relapses have a very poor prognosis
- C-MYC translocation	poorer outcome; consider clinical trials +++
In some reports	
- PET before ASCT transplant	usually recommended to perform ASCT in PET negative patients[21]
- GCB/non-GCB tumor phenotype	might consider different regimen or targeted agents
- Bcl2 and Myc protein co-expression	to be confirmed in future studies
- Refractoriness during first line therapy	ultra-high risk patients; consider clinical trials +++

IPI, International Pronostic Index; NCCN-IP, National Comprehensive Cancer Network-IPI; PET-CT, Positron emission tomography–computed tomography; GCB, Germinal Center B-cell; ASCT, Autologous Stem Cell Transplant.

tes (against CD22, CD79) or bispecific antibodies, may be used in all DLBCL subtypes, while other, such as IMIDs, inhibitors of the BCR (BTKi and PI3Ki), inhibitors of EZH2, inhibitors of the bromodomain or inhibitors of Bcl2 may only be effective in certain patients with specific tumor characteristics. Likely, these drugs need to be combined with standard cytotoxic regimens or eventually with each other. Immune checkpoint blockers have a limited effect as single agents in DLBCL, but a large randomized European study will soon be launched evaluating nivolumab in combination with R-GemOx. But the preliminary results of engineered CAR-T cell appear to open new avenues in the management of R/R DLBCL.[20] Even if optimizing the efficacy and tolerability CAR-T remains necessary, it is likely that these new cellular therapy approaches will play a role in certain group of patients with R/R DLBCL, eventually as a new option at first salvage therapy.

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