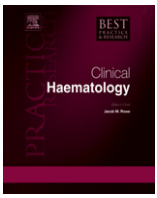
Best Practice & Research Clinical Haematology 25 (2012) 49–60

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha



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Relapses, treatments and new drugs

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Keywords:
diffuse large B-cell lymphoma
salvage chemotherapy
monoclonal antibody
small-molecule inhibitors

We now better understand that the treatment of Diffuse Large B-cell lymphoma (DLBCL) must take into account individual factors related to the biological characteristics of tumors and patients. Treatment failure has dramatically reduced with the combination of rituximab and chemotherapy, mostly in the germinal center B (GCB) cell-like subset. However, salvage chemotherapy and auto-transplantation are less effective in patients with previous exposure to rituximab. Therefore, new therapies should focus on poor-risk patients or on the non-CG subset.

After reviewing the recent data on salvage strategy, we aimed to focus on novel agents that have been shown to be promising for future therapy of DLBCL (e.g., monoclonal antibody-based therapy and small-molecule inhibitors) and, lastly, to present perspectives on the use of these new agents in combination.

Introduction

We now better understand that the treatment of Diffuse Large B-Cell lymphoma (DLBCL) must take into account individual factors related to the biological characteristics of tumors and patients. A more comprehensive and global view of the molecular heterogeneity of the tumor and of the host response will help us to design more rational approaches to successfully treat these patients by targeted therapies or stem-cell transplantation.

The rate of relapse and failure was dramatically reduced with the combination of rituximab and chemotherapy, but patients who relapse or fail to achieve a complete remission (CR) have a poor outcome with a life expectancy of 6 months. Because less than 10% of these patients obtain long-term

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doi:10.1016/j.beha.2012.01.002

disease-free survival with a salvage regimen alone, there is an unmet need for this population, and new drugs should be evaluated more quickly. However, despite the large amount of data collected in the last 10 years by genome-wide analyses, only a few identified targets have progressed to phase II trials for DLBCL [1,2].

After reviewing the recent data on salvage strategies, we aimed to focus on novel agents that have been shown to be promising for future therapy of DLBCL and, lastly, to present perspectives on the use of new agents in combination.

Relapse treatments

The relapse paradigm

All patients are now treated with frontline rituximab and chemotherapy (Fig. 1). The analysis of randomized studies and registry data from patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) confirmed that a major improvement in the treatment of DLBCL is observed in the general population. Fewer relapses are seen among patients with 0–2 International Prognostic Index (IPI) factors (10–20%); however, 50% of relapses are seen in patients with more than 2 IPI factors. In the absence of transplantation, the outcome of relapsing patients is still poor. In the long-term analysis of data from the LNH 98-5 trial, comparing CHOP and R-CHOP in patients over the age of 60 years, median overall survival (OS) after progression was 0.6 months and 0.7 months for CHOP and R-CHOP, respectively [3].

In younger or fit elderly patients, the initial approach to relapsed DLBCL management is to determine whether the patient is a candidate for high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT). In 1995, the PARMA trial evaluated salvage chemotherapy with platinum and cytarabine (DHAP) alone or in combination with ASCT [4]. Both Event-Free Survival (EFS) and OS were significantly superior in the ASCT vs. chemotherapy group. Based on these results, ASCT has become the standard of care in younger patients with chemosensitive relapsed or primary refractory aggressive lymphoma. Induction therapy before ASCT consists of salvage regimens. Several important issues related to obtaining the best CR are still in question: first, the type of salvage regimen to choose; second, the efficacy of rituximab used in an era when R-CHOP is accepted as standard care in frontline therapy; third, the risk factors for second line age-adjusted IPI (s-aaIPI) or relapse less than 12 months from diagnosis. When the patient is not a candidate for ASCT, other therapeutic options such as new biological therapies may be considered. Improvements in outcome may potentially be achieved through a greater understanding of the genetic abnormalities specifically associated with poor prognosis and of factors that lead to chemotherapy failure.

Selecting a salvage regimen

Various old and new drugs are treatment options for DLBCL in the salvage setting. The effectiveness of these agents has been evaluated mainly in non-randomized studies, and the difficulty of obtaining

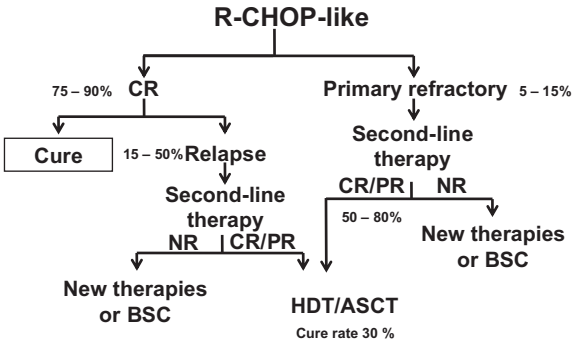

Fig. 1. Management of DLBC lymphoma.