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Dose adjusted R-EPOCH and other etoposide-containing regimens in first-line treatment of diffuse large B-cell lymphoma

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Abstract

Etoposide is a well-known cytotoxic agent effective in the treatment of B-large cell lymphoma (B-LCL). Currently, there is no consensus regarding the place of etoposide-containing regimens (R-CHOEP, R-ACVBP and DA-R-EPOCH) in front-line treatment of B-LCL. This paper summarizes published data and our own experience regarding the activity and toxicity of these regimens, especially DA-R-EPOCH. Most non-randomized, real-life and retrospective studies suggest that, compared to R-CHOP, DA-R-EPOCH, similarly to other etoposide-containing regimens, has superior antitumor efficacy but is also more toxic. The most important severe side-effects are hematological and infectious, making the regimen unfeasible in unfit patients. However, in fit patients with high-risk features, progression-free survival rates seem improved by 15–20% compared to R-CHOP. In our series of high-risk [age-adjusted International Prognostic Index (aaIPI) 2–3] fit [Eastern Cooperative Oncology Group (ECOG) performance status 0–2]) B-LCL patients older than 60 treated with DA-R-EPOCH, PFS at 2 years was 70%, while it was 53% in a comparable historical cohort treated with R-CHOP. DA-R-EPOCH resulted in more hematological and infectious toxicity, but no treatment-related mortality. In our opinion, DA-R-EPOCH should be considered in newly diagnosed, fit, high-risk patients with B-LCL who are older than 60, provided that there is adequate outpatient supervision, supportive care, and prompt hospital admittance in case of neutropenic fever or other severe toxicities.

Key words: diffuse large B-cell lymphoma, etoposide, elderly

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Introduction

B-large cell lymphoma (B-LCL) is the most common type of non-Hodgkin lymphoma (NHL); diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) is its most common variant, with an incidence of around 4.5 per 100,000 [1]. The disease occurs in all age groups, including children. Immunochemotherapy is the mainstay of front-line treatment, and trials with newer agents have so far failed [2, 3]. However, there is no consensus on the choice of optimal chemotherapy regimen. Too often in international meetings one hears it suggested that R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and steroids) is the standard front-line treatment for this disease. While this might be true according to the National Comprehensive Cancer Network (NCCN) guidelines [4], it is not the case according to European recommendations which list two additional options for younger, high-risk patients [age below 60, age-adjusted International Prognostic Index (aaIPI) 2–3]: R-CHOEP14 and R-ACVBP [5].

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Less than 60% of patients with high-risk disease, defined as aaIPI ≥2 or International Prognostic Index (IPI) 4–5, can be cured with R-CHOP. In contrast, multiple case series and phase II trials, as well as a phase III trial, have shown that R-CHOEP14 and R-ACVBP result in progression-free survival (PFS) above 75%, which seems to be 15–20% higher than what can be achieved with R-CHOP [6]. These etoposide-containing regimens result in more acute toxicity, but no treatment-related mortality, and also carry a somewhat increased risk of late toxicities, including secondary tumors and cardiac disease. Still, the net effect seems to be positive, at least in high-risk patients below the age of 60. For instance, our cohort of B-LCL patients with aaIPI ≥2 treated with R-CHOEP14 had 5-year OS of 90% and PFS of 87% which, to the best of our knowledge, has never been reported with R-CHOP [6]. The role of DA-R-EPOCH in this context is less well defined.

DA-R-EPOCH

DA-R-EPOCH is a regimen devised by the National Cancer Institute (NCI), consisting of the same drugs as CHOEP [7, 8]. Instead of administering cytotoxic agents in fixed dosed short infusions or as a bolus, etoposide, doxorubicin and vincristine are administered by continuous infusion over four days. The dose of cytotoxic agents is titrated according to hematologic toxicity, in order to achieve severe granulocytopenia lasting less than a week without severe thrombocytopenia. The acceptance of this regimen has been hindered by its complexity. In many countries, continuous 4-day infusion can be performed only in hospital. Patients need to check their blood counts at least twice a week and attending physicians need to be aware of these findings (and dose adjustment rules) when prescribing the next treatment cycle. On the other hand, continuous infusion of doxorubicin is less cardiotoxic than the standard way of administration, making this regimen feasible in fit patients with borderline cardiac function and those who have been pretreated with standard CHOP [7].

DA-R-EPOCH is more toxic than R-CHOP, resulting in significantly more grade 3–4 hematological and infectious side-effects, but also more mucositis and neuropathy. Prospective clinical trials usually show no difference in treatment-related mortality in fit patients.

NCCN lists DA-R-EPOCH as the recommended standard regimen for primary mediastinal B-cell lymphoma (PMBCL) based on a phase II study performed mainly in the NCI [9]. PMBCL is different from DLBCL NOS in some respects, but similarly responds to immunochemotherapy when adjusted for main prognostic factors, IPI and bulk; the results of NCI using DA-R-EPOCH in DLBCL-NOS were also excellent. One might therefore question whether treatment recommendations for immunochemotherapy for the two entities should really be different.

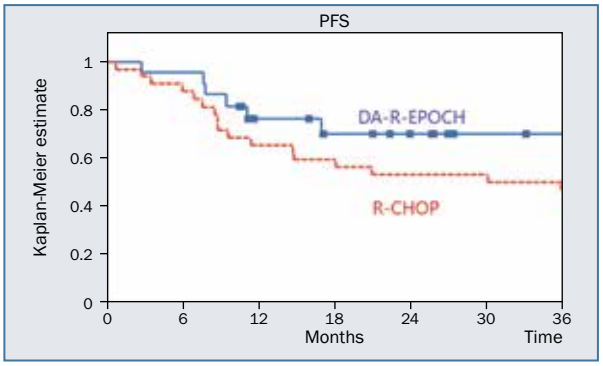

Figure 1. Progression-free survival (PFS) of high-risk elderly patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 treated with R-CHOP (red line) or DA-R-EPOCH (blue line); p =0.2 [15]

Phase II studies of DA-R-EPOCH resulted in outcomes that seem superior to what can be achieved with R-CHOP [8, 10–13]. This was not borne out by a large randomized clinical trial performed in the USA comparing these two regimens [14]. PFS and OS were largely similar in the two treatment arms. However, PFS of the subgroup of patients with IPI 3–5 treated with DA-R-EPOCH was 15–20% better, a statistically significant and clinically meaningful difference. Additional analysis of non-randomized studies, comparing outcomes of DA-R-EPOCH and R-CHOP, suggest that the advantage of the former is mainly limited to high-risk fit patients.

Based on these findings, we started using DA-R-EPOCH in high-risk patients older than 60 [15]. In our experience, cytotoxic drug dose can be increased in only 35% of patients. We found the regimen to be unfeasible in patients with ECOG performance status of 3–4 who had an unacceptably high frequency of toxic deaths (5 out of 9). In contrast, in the 22 patients with ECOG performance status 0–2, the regimen had significant toxicity, but was feasible and so far without toxic deaths. In that group, granulocytopenia was universal by design, anemia grade 3–4 occurred in 23%, thrombocytopenia in 14%, and infections in 77%. 86% of fit patients responded to DA-R-EPOCH, and 64% achieved complete remission. After a median follow-up of 22 months, 2-year PFS was 70%, which compares favorably to outcomes of a comparable historical cohort treated with R-CHOP that had a 2-year PFS of 53%, but failed to reach statistical significance (Figure 1). KroHem, the Croatian Cooperative Group for Hematologic Disease, collected data on the outcomes of 103 newly diagnosed high-risk B-LCL patients older than 60 who were treated with DA-R-EPOCH in Croatian hospitals. The results were largely similar as in our single-center experience. 79% of patients responded: 2-year PFS of fit (ECOG performance status 0–2) patients was 67% and of unfit (ECOG performance status 3–4) patients was 44% [16].

Discussion

Discussions as to the role of etoposide in front-line treatment of DLBCL have continued for a number of years and remain unresolved. Medical evidence 'purists' point to the lack of randomized trials (usually neglecting the French trial comparing R-ACVBP to R-CHOP in younger intermediate risk patients). And while performing a randomized trial in the proper patient population might seem the best approach, current rules and regulations and the availability of commercially sponsored trials with new agents make this idea unrealistic. However, in our opinion, the preponderance of available data suggests that front-line regimens containing etoposide: R-CHOEP14, R-ACVBP and DA-R-EPOCH, have superior anti-tumor activity compared to standard R-CHOP in DLBCL. On the other hand, these regimens are also more toxic, making them unsuitable for unfit patients and those with low risk disease. In order to enjoy the benefit of increased efficacy without undue treatment-related mortality, more intensive supervision than is usual with R-CHOP during the whole treatment period, and the possibility of prompt admittance and in-hospital treatment of infectious, and to a lesser extent other, complications is of paramount importance.

Conclusions

A significant number of patients might benefit from the addition of this inexpensive agent. The magnitude of potential clinical benefit (15–20% increase in PFS and 10–15% in OS), is similar to, or higher than, that seen in phase II trials of new and expensive agents such as polatuzumab and venetoclax [17, 18].

These are valid arguments for at least considering etoposide-containing regimens in appropriate patients. Therefore, KroHem, the Croatian Cooperative Group for Hematologic Diseases, recommends treating fit patients with newly diagnosed high-risk DLBCL with R-CHOEP14 or DA-R-EPOCH.

Author's contributions

IA — sole author.

Conflict of interest

None.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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