High dose intensity doxorubicin in aggressive non-Hodgkin’s lymphoma: a literature-based meta-analysis

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Background: Aggressive non-Hodgkin’s lymphoma (NHL) represents ~60% of lymphomas in the West and even more in the developing world. Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is recognized as the standard chemotherapy regimen and the addition of rituximab to B-cell subtypes has been shown to significantly improve treatment outcomes. Nevertheless, still a significant fraction of patients is not offered rituximab due to economic reasons. Thus, CHOP is still offered to these patients as well as those with T-cell subtypes. Data from the early 1990s have indicated that the dose intensity (DI) of doxorubicin is a key factor in predicting survival.

Methods: A Medline and Cochrane library search was carried out using the search terms ‘CHOP’, ‘lymphoma’ and ‘randomized trials’. Eligible trials had CHOP as a control arm and any regimen administering doxorubicin at a higher DI (16.6 mg/m²/week) as the investigational arm. Pooling of data was carried out using the mixed effect model.

Results: Eight trials were eligible. Patients receiving DI doxorubicin-based regimens had a significantly better overall survival (summary hazard ratio (SHR) 0.82; 95% confidence interval (CI) 0.71–0.96), event-free survival (SHR 0.86; 95% CI 0.75–0.99) and higher complete response rate (summary odds ratio 0.91; 95% CI 0.67–0.97).

Conclusion: High DI doxorubicin based should be considered in patients with aggressive NHL.

Key words: chemotherapy, CHOP, dose intensity, doxorubicin, non-Hodgkin’s lymphoma

Introduction

Aggressive non-Hodgkin’s lymphomas (NHLs) represent ~60% of lymphomas in the Western world and even a greater proportion in other developing nations [1, 2]. Nearly all patients receive systemic therapy as primary treatment, and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP; recycled day 21) is recognized as the standard chemotherapy regimen in this disease [1]. B-cell subtypes represent ~80% of aggressive NHL, and in this group, the addition of rituximab to CHOP (R-CHOP) has resulted in a significant improvement in response rates, event-free survival (EFS) and overall survival (OS) [3,4]. Nevertheless, a significant proportion of patients in the developing world is not offered rituximab due to economic reasons. Moreover, and since its introduction, little concern has been given to the scheduling of chemotherapy.

In the late 1980s and early 1990s, there was widespread interest in the concept of dose intensity (DI), the amount of chemotherapeutic drug delivered per unit time, as a potential factor-affecting outcome. A retrospective analysis from Stanford University evaluated the prognostic importance of relative DI of chemotherapeutic agents in 115 patients with diffuse large-cell lymphoma [5]. In this study, the amount of drug actually administrated to each patient during the first 12 weeks of therapy was calculated and analyzed in addition to other known clinical prognostic factors. In the multivariate analysis, attaining an actual relative DI of doxorubicin of >75% was the single most important predictor of survival. This study, in spite of its retrospective nature, highlighted two important points. The first is the importance of doxorubicin in treating aggressive NHL. This observation has been further demonstrated in several studies where deleting or replacing doxorubicin has resulted in inferior outcomes [6–8]. The second is the importance of DI and that higher relative DI of doxorubicin might be associated with superior results. Several trials have tried to address this point with conflicting results.

Hence, we conducted a meta-analysis of published randomized controlled trials comparing chemotherapy regimens incorporating doxorubicin at a high DI (>16.6 mg/m²/week) with standard CHOP.

Methods

The study design was a quantitative synthesis of randomized controlled trials that could contribute to the evaluation of the impact of DI doxorubicin-based regimens in aggressive NHL and whether or not such...
regimens could be superior to CHOP. The primary end points were 5-year EFS and OS. Complete response (CR) rate was evaluated as a secondary end point. OS was defined as time from randomization to death or last follow-up date while EFS was defined as time from randomization to progression, relapse, death or last follow-up date. CR was defined as disappearance of all visualized disease or reduction in >90% of the disease with an unconfirmed nature of the residual lesions (CRu).

**data sources, search strategy and selection of articles**

The search was carried out for clinical trials, and no language or time restrictions were applied. The literature up to February 2008 was searched using the Medline and Cochrane library databases. Studies not reported in full text (abstract only) were not considered eligible. For study population and methods, the following key words were used: ‘lymphoma’ and ‘randomized trial’. For study intervention, the following key words were used: ‘CHOP’ and/or ‘chemotherapy’. At first a general search was carried out using the study population key word alone (i.e. lymphoma), then a combination of key words for population, intervention and methods was carried out.

Primary inclusion criteria were developed for the selection of all relevant articles, which were independent randomized trials (phase II and phase III) published as an original article for NHL having CHOP as a control arm. Retrospective studies, reviews and editorials were not considered eligible. Based on these primary inclusion criteria, the initial relevance of all retrieved articles was evaluated by two of the authors (HAA and RAM) based on the title and abstract.

In the next step, the results were reviewed by a third author (RGB) and some further criteria were developed in an attempt to obtain a homogenous group of studies, each with at least minimal information and comparable results:

- The investigational regimen had to be a doxorubicin-based regimen administering doxorubicin at a DI higher than that of CHOP (16.6 mg/m²/week).
- Studies administering any biological agent (rituximab, interferon, etc …) and/or consolidation with bone marrow transplant in the investigational arm were excluded.
- Studies restricted to patients with low-grade lymphomas were excluded.
- Studies restricted to patients with localized disease were excluded.
- The studies had to provide sufficient information to estimate the odds ratio (OR), relative risk (RR) and 95% confidence interval (CI) (i.e. they had to publish the OR or RR or crude data and corresponding standard errors, variance, CIs or P value of the significance of the estimates).

**description of studies retrieved**

After checking for primary inclusion criteria for relevance in terms of study design (independent randomized trials), outcome definition, control group definition (NHL having CHOP as a control arm) and after exclusion of repetitions, 60 trials were identified. After applying the secondary exclusion criteria, further 52 trials were considered ineligible for various reasons (Figure 1). The remaining eight trials met all the eligibility criteria and were included in this meta-analysis [9–16]. All of them were entered into a randomized phase III trials. The results of five trials were provided from their original publication [11,13–16] while updated versions of original papers [17–19] were used in the rest in order to provide longer follow-up results [9, 10, 12].

**statistical analysis**

Denominators used for calculating CR rate, EFS and OS in each treatment group were those classified as eligible patients coming from randomization. The B1 and B2 German studies [13, 14] were planned as 2 × 2 factorial designs to test two independent factors: interval reduction (comparing all patients randomized to 2-weekly regimens with those to 3-weekly regimens) and addition of etoposide (comparing all patients randomized to CHOP regimen with all patients randomized to CHOEP). Since the B1 study [13] did not show any synergic or antagonist interaction between the two study factors, we included all randomized patients in the present meta-analysis. All patients related to the 3-weekly regimen group were then considered as coming from the CHOEP21 ‘control’ group and all patients related to the 2-weekly regimen group were considered as coming from the CHOEP14 ‘intervention’ group. In the B2 study, on the contrary, the authors found an interaction between the two main factors. For this reason, we focused on the two nonindependent comparisons with CHOP regimen as control group and the two 2-weekly regimens (CHOEP14 and CHOEP14) as intervention groups and the CHOEP21 arm was excluded.

The association between exposure (treatment) and outcome was measured by OR for the CR rate and by hazard ratio (HR) for EFS and OS. In these time-related events, no distinctions were made between the various measures of association (RR, rate ratio, risk ratio and HR).

When the OR and 95% CIs were available, we transformed them into log(OR) and calculated the corresponding variance and standard error using the formula proposed by Greenland [20]. When the OR was not directly available from paper, we calculated it from tabular data, using the Woolf formula to evaluate the standard error of the log(OR) [21]. If tabular data were not given and only response rate was available, the number of responses was calculated by multiplying the response rate by the number of randomized/eligible patients. Summary statistics for survival end points were extracted using the methods of Parmar et al. [22]. When the HR and pertinent 95% CIs were available, we transformed them into log(HR) and calculated the corresponding variance and standard error. When not directly available, the log(HR) and its standard error were indirectly calculated from the reported HR with the number of events, from the reported number of events with the P value or the χ² value for the treatment effect or from the survival curves.

The association between higher DI and response rate across the selected trials was computed as summary odds ratio (SOR) with 95% CI. The SOR was considered statistically significant if the 95% CIs did not include 1.0. Similarly, the association between higher doxorubicin DI and EFS/OS was computed as summary hazard ratio (SHR) with 95% CI. SOR and SHR were estimated pooling the study-specific estimates by random effect models fitted using SAS (proc Mixed) with maximum likelihood estimate.
These models provided estimates adjusted for the correlation within studies (B1 and B2 trials) as well as the heterogeneity between studies. Concerning this point, despite that the B1 and B2 studies were published separately, in our meta-analysis they were analyzed as two subgroups of a single trial. They were published by the same group, in the same year, with the same study design administering the same interventions. This is a conservative approach, which provides wider and more reliable CIs.

Heterogeneity of the effect across studies was assessed by the $I^2$ statistics. A $P$ value <0.10 was used to indicate lack of homogeneity among effects. $I^2$ statistics was also provided to quantify the percentage of total variation across studies that were attributable to heterogeneity rather than to chance [23]. The method of Macaskill et al. [24] was used for assessing publication bias. It consists of a funnel-plot regression of log(RR) or log(OR) on the sample size, weighted by the inverse of the pooled variance.

**results**

**characteristics of the trials**

Our analysis included 3853 patients randomly assigned to either CHOP (1845 patients) or DI doxorubicin-based regimen (2008 patients). The number of subjects enrolled in the different studies varied from 236 to 710. Mean follow-up varied between 49 and 80 months. Table 1 summarizes the characteristics of the eligible studies.

In the eight studies, six investigational regimens were used namely MACOP-B, CHOP14, CHOEP14, I-CHOP, PACEBOM and ACVBP with a doxorubicin DI of 25, 25, 25, 35, 17.5 and 25 mg/m$^2$/week, respectively.

Two studies [14, 15] included only patients >60, while one study [13] included only patients <61. The remaining five studies had no age restriction [9–12, 16]. CHOP was given for six cycles in three studies [9, 13, 14], eight cycles in two studies [15, 16] and from six to eight cycles in three studies [10–12]. In the study by Fisher et al. [9], two of the four study arms were regimens (m-BACOD and ProMACE–CytaBOM) utilizing doxorubicin at a lower DI than that used in CHOP (15 and 12.5 mg/m$^2$/week, respectively); thus, these two arms were excluded from our analysis.

**overall survival**

All studies were eligible for the 5-year OS analysis. HR and 95% CI were published in three trials [13–15]. In the remaining studies, they were extracted from the published survival curves [9–12, 16].

Table 1. Trials comparing CHOP to dose intense doxorubicin-based regimens in aggressive NHL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year of publication (original paper)</th>
<th>Median follow-up (months)</th>
<th>B cell (%): subtype of NHL (DLCBL) (%)</th>
<th>High intermediate/high-risk IPI (%)</th>
<th>Sample size based on: Primary and secondary end points presented</th>
<th>Regimen No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfremundsuh et al. [13]</td>
<td>2003</td>
<td>58</td>
<td>18–60 85.5</td>
<td>59.8</td>
<td>2-Year EFS</td>
<td>EFS, CR, OS</td>
</tr>
<tr>
<td>Pfremundsuh et al. [14]</td>
<td>2003</td>
<td>58</td>
<td>61–75 94.2</td>
<td>70.3</td>
<td>2-Year EFS</td>
<td>EFS, CR, OS</td>
</tr>
<tr>
<td>Verdonck et al. [16]</td>
<td>2006</td>
<td>50</td>
<td>16–65 88</td>
<td>64.1</td>
<td>35$^a$</td>
<td>CR, OS</td>
</tr>
<tr>
<td>Total number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$According to the age adjusted IPI.

CHOP, cyclophosphamide 750 mg/m$^2$/day 1, doxorubicin 50 mg/m$^2$/day 1, vincristine 1.4 mg/m$^2$/day 1, prednisone 100 mg days 1–5, recycle day 21; NHL, non-Hodgkin’s lymphoma; DLCBL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; NR, not reported; CR, complete response (either confirmed or unconfirmed); TTF, time-to-treatment failure; EFS, event-free survival; OS, overall survival; MACOP-B, methotrexate 400 mg/m$^2$/days 8 + 36 + 64, doxorubicin 50 mg/m$^2$/days 1 + 15 + 29 + 43 + 57 + 71, cyclophosphamide 350 mg/m$^2$/days 1 + 15 + 29 + 43 + 57 + 71, vincristine 1.4 mg/m$^2$/days 8 + 22 + 36 + 50 + 64 + 78, bleomycin 10 mg/m$^2$/days 8 + 22 + 36 + 50 + 64 + 78, bleomycin 10 mg/m$^2$/days 22 + 50 + 78, prednisone 75 mg days 1–70; CSS, cause specific survival; DFS, disease-free survival; PACBOM, prednisolone 50 mg days 1–18, 25 mg days 28–84, doxorubicin 35 mg/m$^2$/days 1 + 15 + 29 + 43 + 57 + 71, cyclophosphamide 300 mg/m$^2$/days 1 + 15 + 29 + 43 + 57 + 71, etoposide 150 mg/m$^2$/days 1 + 15 + 29 + 43 + 57 + 71, bleomycin 10 mg/m$^2$/days 8 + 22 + 36 + 50 + 64 + 78, vincristine 1.4 mg/m$^2$/days 8 + 22 + 36 + 50 + 64 + 78, methotrexate 100 mg/m$^2$/days 8 + 22 + 36 + 50 + 64 + 78; CHOEP14, cyclophosphamide 750 mg/m$^2$/day 1, doxorubicin 50 mg/m$^2$/day 1, vincristine 1.4 mg/m$^2$/day 1, etoposide 100 mg/m$^2$/day 1, prednisone 100 mg days 1–5, recycle day 14; CHOP14, cyclophosphamide 750 mg/m$^2$/day 1, doxorubicin 50 mg/m$^2$/day 1, vincristine 1.4 mg/m$^2$/day 1, prednisone 100 mg days 1–5, recycle day 14; CHOEP14, cyclophosphamide 1000 mg/m$^2$/day 1, doxorubicin 70 mg/m$^2$/day 1, vincristine 2 mg day 1, prednisone 100 mg days 1–5, recycle day 14; ACVBP, doxorubicin 75 mg/m$^2$/day 1, cyclophosphamide 1200 mg/m$^2$/day 1, vindesine 2 mg/m$^2$/days 1 + 5, bleomycin 10 mg days 1 + 5, prednisone 60 mg/m$^2$/days 1–5, recycle day 21.
In one study [9], we used the original report results, whose survival curves, though not updated, were long enough to estimate the 5-year OS [17]. In order to extract the log(PR) estimates in the Nordic study, we contacted the corresponding author and obtained the survival estimates data, as the published survival curves were indistinguishable [11]. In other trials, 5-year HR and pertinent 95% CI were extracted from published survival curves because summary results were given at 8 and 6 years, respectively [12, 16]. Table 2 summarizes the 5-year OS results.

Patients who received the DI doxorubicin-based regimen had a significantly better OS compared with those who received CHOP (SHR 0.82; 95% CI 0.71–0.96, \( P = 0.02 \)) (Figure 2). A look at the individual trials indicates that three of eight studies [13–15] demonstrated a significant survival advantage for DI regimens, four [10–12, 16] had a trend favoring DI regimens [13–15] while in the others the log(OR) and its standard error were indirectly calculated from the absolute number of responses. Patients receiving DI doxorubicin-based regimen had event-free survival

Seven of eight studies were eligible for the EFS analysis [9–11, 13–16]. In the study by Linch et al. [12], the EFS analysis was not reported. HR and 95% CI were published in three trials [13–15] and were extracted from the survival curves in the remaining four [9–11, 16]. Table 2 summarizes the results of EFS results. Our results showed a significantly superior 5-year EFS for patients who received the DI doxorubicin-based regimens; compared with those receiving CHOP (SHR 0.86; 95% CI 0.75–0.99) (Figure 3). There was no heterogeneity between trials (\( P = 0.13; \hat{I}^2 = 37.2\% \)) or evidence of publication bias (\( P = 0.89 \)).

CR rates

Response rates were assessed in four trials [9–12] by the World Health Organization criteria [25] while the other four [13–16] used the International Working Group criteria [26]. Four studies considered unconfirmed CR (Cru) in the CR rate analysis [13–16]. Tumor response assessment was made at the end of therapy in four studies [9, 13–15], while two had an interval assessment after the third cycle [10, 16] and two had an interval assessment after the fourth cycle [11, 12]. All studies were eligible for the CR rate analysis and are summarized in Table 2. In two studies, the value of OR and pertinent variance (or 95% CIs) were directly reported by the authors [13, 14], while in the others the log(OR) and its standard error were indirectly calculated from the absolute number of responses.

Patients receiving DI doxorubicin-based regimen had

## Table 2. Methods of estimating HR for OS and EFS and OR for CR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>OS 5-Year OS (%)</th>
<th>HR from paper</th>
<th>HR from KM curves</th>
<th>EFS 5-Year EFS (%)</th>
<th>HR from paper</th>
<th>HR from KM curves</th>
<th>CR (%)</th>
<th>OR from paper</th>
<th>OR from number of responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al. [9, 17]</td>
<td>CHOP</td>
<td>35</td>
<td>✓</td>
<td>✓</td>
<td>39</td>
<td>✓</td>
<td>✓</td>
<td>44</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Wolf et al. [10]</td>
<td>MACOP-B</td>
<td>47</td>
<td>✓</td>
<td>✓</td>
<td>30</td>
<td>✓</td>
<td>✓</td>
<td>51</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Jerkeman et al. [11]</td>
<td>CHOP</td>
<td>54</td>
<td>✓</td>
<td>✓</td>
<td>42</td>
<td>✓</td>
<td>✓</td>
<td>51</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Linch et al. [12]</td>
<td>CHOP</td>
<td>59</td>
<td>✓</td>
<td>✓</td>
<td>44</td>
<td>✓</td>
<td>✓</td>
<td>41</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pfreundshuh et al. [13]</td>
<td>PACEROM</td>
<td>55</td>
<td>✓</td>
<td>✓</td>
<td>48</td>
<td>✓</td>
<td>✓</td>
<td>64</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pfreundshuh et al. [14]</td>
<td>CHOP(e)P</td>
<td>79.2</td>
<td>✓</td>
<td>✓</td>
<td>62.1</td>
<td>✓</td>
<td>✓</td>
<td>82.5</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pfreundshuh et al. [14]</td>
<td>CHOPE14</td>
<td>85</td>
<td>✓</td>
<td>✓</td>
<td>71.6</td>
<td>✓</td>
<td>✓</td>
<td>61</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tilley et al. [15]</td>
<td>CHOP</td>
<td>40.6</td>
<td>✓</td>
<td>✓</td>
<td>43.8</td>
<td>✓</td>
<td>✓</td>
<td>41.2</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Verdonck et al. [16]</td>
<td>CHOP</td>
<td>49.8</td>
<td>✓</td>
<td>✓</td>
<td>40.2</td>
<td>✓</td>
<td>✓</td>
<td>58</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

HR, hazard ratio; OS, overall survival; EFS, event-free survival; OR, odds ratio; CR, complete response; KM, Kaplan–Meier; CHOP, cyclophosphamide 750 mg/m² day 1, doxorubicin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, prednisone 100 mg days 1–5, recyle day 21; MACOP-B, methotrexate 400 mg/m² days 8 + 36 + 64, doxorubicin 50 mg/m² days 1 + 15 + 29 + 43 + 57 + 71, cyclophosphamide 550 mg/m² days 1 + 15 + 29 + 43 + 57 + 71, vincristine 1.4 mg/m² days 8 + 22 + 36 + 50 + 64 + 78, bleomycin 10 mg/m² days 22 + 50 + 78, prednisone 75 mg days 1–70; PACEROM, prednisolone 50 mg days 1–18, 25 mg days 28–84, doxorubicin 35 mg/m² days 1 + 15 + 29 + 43 + 57 + 71, cyclophosphamide 300 mg/m² days 1 + 15 + 29 + 43 + 57 + 71, bleomycin 10 mg/m² days 8 + 22 + 36 + 50 + 64 + 78, vincristine 1.4 mg/m² days 8 + 22 + 36 + 50 + 64 + 78, methotrexate 100 mg/m² days 8 + 22 + 36 + 50 + 64 + 78; CHOPE14, cyclophosphamide 750 mg/m² day 1, doxorubicin 50 mg/m² day 1, vincristine 1.4 mg/m² day 1, etoposide 150 mg/m² ± 25 mg days ± 84, doxorubicin 50 mg/m² day 1, cyclophosphamide 50 mg/m² day 1, bleomycin 10 mg/m² day 1 + 5, prednisone 60 mg/m² ± 1 ± ± 70 mg/m², prednisone 100 mg days 1–5, recycle day 21; I-CHOP, cyclophosphamide 1000 mg/m² day 1, doxorubicin 70 mg/m² day 1, vindesine 2 mg/m² days 1 ± 5, bleomycin 10 mg days 1 ± 5, prednisone 60 mg/m² days 1–5, recycle day 21; ✓, information reported on the article.
a significantly higher CR rate (SOR 0.81; 95% CI 0.67–0.97) (Figure 4). There was no heterogeneity between trials \( (P = 0.12; \ I^2 = 38.0\%) \) or evidence of publication bias \( (P = 0.64) \).

**sensitivity analysis**

We carried out a sensitivity analysis by excluding patients who were exposed to etoposide in the B1 and B2 studies. CR rate, EFS and OS remained significantly better in favor of DI regimens (Table 3).

In an attempt to examine whether or not a certain International Prognostic Index (IPI) risk group benefits the most of the DI approach, we carried out another sensitivity analysis by excluding the B1 study, which was the only study restricted to young patient with favorable prognosis. The results showed a more pronounced OS advantage with decreased heterogeneity between the trials. This result remained consistent when the two studies \[9, 12\] with unreported data on IPI score were excluded as well (Table 3).

**discussion**

This current analysis evaluated the effectiveness of DI doxorubicin-based regimens in treating patients with aggressive NHL. We found that patients receiving DI regimens had significantly higher EFS and OS with an 18% reduction in the risk of death. Moreover, patients who received DI regimens had
a 19% higher chance in attaining a CR compared with those who received CHOP.

In three studies that demonstrated a significant difference in survival [13–15], the benefit of DI regimens was seen in both low- and high-risk patients. However, subgroup analysis of two other studies [10, 11] showed restricted benefit of DI regimens in high-risk patients (IPI >2). In an attempt to consolidate this finding, we carried out a sensitivity analysis by excluding the B1 trial, which was restricted to low-risk patients. The results showed that DI regimens remain significantly superior to CHOP.

R-CHOP is the standard of care in treating patients with aggressive B-cell lymphoma patients [3, 4]. The addition of rituximab to a DI doxorubicin-based regimen (CHOP14) has recently been shown to be superior to CHOP14 alone in all treatment end points [27]. Yet, no direct comparison is available between a DI doxorubicin-based regimen and classic R-CHOP. Thus, for clinical situations where it is not possible to use rituximab (e.g. for economic reasons), DI doxorubicin-based regimen should be considered.

In the interpretation of our results, it is important to recognize the absence of quality of life (QoL) or toxicity analyses. QoL was assessed only in the Nordic study [11] which showed that patients in the MACOP-B group had a lower global QoL ($P = 0.04$) and physical function ($P = 0.01$) after 12 weeks of therapy compared with CHOP. However, at 56 weeks, there was no residual difference between the two regimens. It was not possible to conduct any rigorous toxicity analysis using our methodology, as adverse events were very heterogeneously reported among the eligible studies. As expected, DI regimens were frequently associated with a higher incidence of neutropenia compared with CHOP, and this difference was statistically significant in nearly all studies. Prophylactic growth factors [granulocyte colony-stimulating factor (G-CSF)] were used in four studies [13–16], but the risk of neutropenia was still higher with the exception of CHOP14, which had a similar rate of neutropenia in the B1 and B2 trials [13, 14]. The risk of neutropenia was seen significantly higher with CHOEP14 [13, 14], I-CHOP [16] and ACVBP [15] despite the use of prophylactic G-CSF. No significant differences were seen with respect to the risk of treatment-related mortality except in one study [15] in which ACVBP doubled the risk of death secondary to chemotherapy ($P = 0.014$).

It is unclear from our analysis the best DI regimen that should be used as well as the number of cycles that should be administered. Putting toxicity and feasibility into perspective, we believe that CHOP14 with G-CSF support appears to be the most suitable. In the B1 [13] and B2 [14] studies, CHOP14 was associated with very comparable toxicity to that of CHOP. There is no evidence of higher hospitalization secondary to neutropenia associated with this regimen. Furthermore, in our sensitivity analysis, by excluding the results of CHOEP14, the superiority of DI regimens remained significant. As for the number of cycles, this was only addressed in the RICOVER trial and it showed that eight cycles of CHOP14 are superior to six cycles in terms of EFS with no difference in OS [27].

It is hard to draw solid conclusions on the best DI regimens according to histology (B cell or T cell). None of the included studies has addressed this point and thus we failed to carry out any sensitivity analysis to address this point. It is important to clarify that the data used for analysis are not individual patient data, which in general give an independent patient database meta-analysis [28], but rather, abstracted data. This methodology is more prone to publication bias and does not allow the performance of certain subgroup analyses to obtain results that are more concise. However, we did not detect any evidence of publication bias using standard statistical methods [24].

Although the eight included studies were randomized phase III trials, not all of them were fully described in terms of

![Table 1: Complete response rate analysis.](Image)
primary end points, power and sample size calculation. In the Nordic study [11], there was no mention of the primary end point on which the sample size calculation had been based on, making it uncertain whether the study was properly powered or not. In the Fisher study [9, 17], neither the study hypothesis (superiority versus equivalence) nor the primary end point (response rate versus time-to-treatment failure) were clearly stated; consequently, no formal sample size calculation was given. The HOVON trial [16] was planned based on two primary end points (CR and OS). In the OS analysis, it was reported that the recruitment period lasted up to 7 years, which was also the maximum follow-up period. It is postulated that patients who were included in the past year or two had a short follow-up period. However, the 6-year OS was estimated indicating a high censoring rate in this study.

We redefined complete remission in our analysis to include patients with CRu, as the latter was the case in four of the studies examined. However, positron emission tomography scan was not used in any of the trials included in this meta-analysis, and given this limitation, CR rate was investigated as a secondary end point.

Despite quite a large heterogeneity in the studies definition, the present meta-analysis provides significant evidences on medium long-term survival based on nearly 4000 patients.

In conclusion, DI doxorubicin-based regimens are associated with better OS. These regimens are also likely associated with greater treatment-related toxicity, and this should be taken in consideration. Based on the results of this analysis, we think it is reasonable to consider this approach in poor-risk patients and those not offered rituximab.

acknowledgements

The authors would like to thank Dr. Mats Jerkeman for providing detailed information regarding the survival analysis of his study [11]. An acknowledgment should also go to Mr. William Russell Edu, the librarian at the European Institute of Oncology, for his efforts in preparing the scientific material required for this work.

disclosure

Honorarium (Roche) to HAA.

references

12. Linch DC, Smith P, Hancock BW et al. A randomized British national lymphoma investigation trial of CHOP vs. a weekly multagent regimen (PACEBOM) in

Table 3. Sensitivity and subgroup analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR/OR (95% CI)</th>
<th></th>
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<tr>
<td>Sensitivity analysis</td>
<td></td>
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<tr>
<td>Exclusion of etoposide arms from B1 and B2 [13, 14] studies</td>
<td>0.82 (0.69–0.98)</td>
<td>40</td>
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<tr>
<td>OS</td>
<td>0.86 (0.74–1.01)</td>
<td>42</td>
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<td>EFS</td>
<td>0.84 (0.70–1.00)</td>
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<tr>
<td>Poor prognosis (exclusion of B1 [13])</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>OS</td>
<td>0.83 (0.71–0.96)</td>
<td>36</td>
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<tr>
<td>EFS</td>
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<td>44</td>
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<tr>
<td>ORR</td>
<td>0.80 (0.64–1.01)</td>
<td>45</td>
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<tr>
<td>Poor prognosis (exclusion of B1 [13] and missing IPI data [9, 12])</td>
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<tr>
<td>OS</td>
<td>0.77 (0.65–0.91)</td>
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<td>EFS</td>
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<td>ORR</td>
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<td>Subgroup analysis</td>
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<td>Year of publication</td>
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<tr>
<td>OS ≤2000</td>
<td>0.91 (0.71–1.17)</td>
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<td>0.41</td>
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<td>&gt;2000</td>
<td>0.74 (0.56–0.98)</td>
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<td>ORR ≤2000 (CR)</td>
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<td>22.3</td>
<td>0.28</td>
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<td>&gt;2000 (CR/CRu)</td>
<td>0.77 (0.49–1.23)</td>
<td>52.1</td>
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</table>

The $P^2$ represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance. HR, hazard ratio; OR, odds ratio; CI, confidence interval; OS, overall survival; EFS, event-free survival; IPI, International Prognostic Index; CR, complete response; CRu, unconfirmed CR.