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ORIGINAL ARTICLE

CHOP-like-14 compared to CHOP-like-21 for patients with aggressive lymphoma – a meta-analysis of randomized controlled trials

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ABSTRACT

Background. R-CHOP-21 has remained the standard chemotherapy for aggressive non-Hodgkin's lymphoma. It was suggested that decreasing the treatment interval from three weeks (CHOP-21) to two weeks (CHOP-14) may improve survival and disease control of patients with aggressive lymphoma.

Purpose. To evaluate the effect of CHOP-like-14 (with or without rituximab) compared to standard CHOP-like -21 on overall survival (OS), disease control and toxicity of patients with aggressive non-Hodgkin lymphoma.

Methods. Systematic review and meta-analysis of RCTs. In October 2014 we searched The Cochrane Library, MEDLINE, LILACS, conference proceedings, and databases of ongoing trials. Authors were contacted for complementary data. The primary outcome was OS.

Results. We identified seven trials (4073 patients), conducted between the years 1999 and 2008. Trials were at low or unclear risk for selection bias, and at low or unclear risk of attrition bias. CHOP-like-14 improved OS of patients with aggressive lymphoma compared to the same regimen given every 21 days (all trials): HR of death 0.86, 95% confidence interval (CI) 0.77–0.97. There was no OS difference between rituximab-CHOP-like 14 to rituximab-CHOP-like-21 (3 trials): HR 0.93 95% CI 0.78–1.10. The rates of progression or death, complete response, treatment-related mortality, grade 3–4 infection, and discontinuation were similar between groups.

Conclusion. R-CHOP-21 remains the standard of care for patient with aggressive B-cell lymphoma. CHOP-14 can be considered as in case rituximab is omitted.

The group of aggressive non-Hodgkin lymphomas includes mainly diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, and peripheral T-cell lymphoma. The most common aggressive lymphoma is DLBCL, accounting for about 40% of lymphomas in adults [1]. The median age at presentation is 64 years. The international prognostic index (IPI) has been extensively used to assess the risk of recurrence of disease and survival in patients with DLBCL. While the five-years overall survival (OS) of patients at low risk (IPI 0–1) is 91% it approaches only 59% in patients at high risk (IPI 4–5) [2,3].

The dose dense regimen is based on mathematical models known as the Gompertzian model (or Norton-Simon hypothesis) of human cancer growth [4]. This model suggests that the reduction of tumor size by chemotherapy is associated with acceleration in growth fraction and growth rate. Administration of chemotherapy at shorter intervals enables it to work on a higher growth fraction. This concept was tested in patients with solid

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tumors and was found to be efficacious in breast cancer [5].

Rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) given every 21 days repeated for 6–8 cycles is considered the standard treatment for patients with aggressive lymphoma [6–9]. It was suggested that decreasing the treatment interval from three weeks (CHOP-21) to two weeks (CHOP-14) may improve survival and disease control of patients with aggressive lymphoma, though toxicity might be higher. Administration of CHOP-14 protocol became possible with the introduction of granulocyte colony-stimulating factors (GCSF), which allowed the chemotherapy courses to be condensed without causing unacceptable toxicity.

A number of randomized controlled trials evaluating the effect of dose densification by reducing treatment intervals from 21 to 14 days were conducted, albeit with conflicting results and as such, the interval between CHOP courses has remained a matter of debate.

We performed a systematic review and meta-analysis to evaluate the efficacy of a dose dense chemotherapy regimen as CHOP-14 or CHOP-like-14 compared to CHOP-21 or CHOP-like-21 on OS, disease control, and toxicity of patients with previously untreated aggressive lymphoma.

Methods

Data sources

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (Issue 2, 2014), Pubmed (1966–October 2014), LILACS (1982–2013), and conference proceedings of the American Society of Hematology (1995–2013), the American Society of Clinical Oncology Annual Meeting (1995–2013), and the European Hematology Association (to 2013), and databases of ongoing and unpublished trials: http://www.controlled-trials.com/, http://www.clinicaltrials.gov/ct, http://clinicaltrials.nci.nih.gov/. We crossed the term 'lymphoma' and similar with the term 'aggressive OR diffuse OR large cell' and similar, and the term 'CHOP OR dose-dense' and similar. We combined the search terms with the highly sensitive search strategy for identifying reports of randomized controlled trials in the MEDLINE search [10]. We scanned references of all included trials and reviews identified for additional studies.

Study selection

We included all randomized, controlled trials including patients with previously untreated histologically confirmed, aggressive lymphoma at age 16 and older, and comparing any anthracycline-based chemotherapy combination given at an interval shorter than 21 days (as CHOP-14 or R-CHOP-14) to the same chemotherapy combination given at the conventional interval (as CHOP-21 or R-CHOP-21). The chemotherapy regimen was identical in the two groups. Rituximab and etoposide could be added to both assigned groups. Supportive care could differ between the study groups.

All types of aggressive lymphoma according to the WHO 2008 classification could be included. We included trials regardless of publication status, date of publication, and language.

Types of outcome measures

The primary outcome was OS. Secondary outcomes were complete remission, event-free survival, progression-free survival (PFS), quality of life, and adverse events. We performed sub-group analyses for the primary outcome by age (≤ 60 years, > 60 years), rituximab use, type of chemotherapy regimen, IPI score, DLBCL.

Data extraction and quality assessment

Two reviewers (LV, AG) independently extracted data regarding case definitions, characteristics of patients, and outcomes from included trials. In the event of disagreement in any of the above between the two reviewers, a third reviewer (OS) extracted the data. Data extraction was discussed and decisions were documented. We contacted the first or corresponding author of each included trial and the researchers who were active in the field to obtain information on unpublished trials or additional information on the published trials. Two reviewers (LV, AG) independently assessed the trials for methodological quality. Allocation concealment, generation of the allocation sequence, blinding, incomplete outcome reporting were individually assessed.

Data synthesis and statistical analysis

Hazard ratios (HRs) and variances for time-to-event outcomes were estimated and pooled according to inverse of variance method [11,12]. A HR less than 1.0 was in favor of CHOP-like-14. Relative risks (RRs) and 95% confidence intervals (CIs) for dichotomous data were estimated using the Mantel-Haenszel method [13].

We assessed heterogeneity of trial results by the χ^2-test of heterogeneity and the I^2 statistic of inconsistency. Statistically significant heterogeneity was defined as p-value < 0.1 or an I^2 statistic $> 50\%$ [14].

Potential sources of heterogeneity were explored through stratifying sub-groups, and quality of trial. We performed sensitivity analysis according to quality of allocation concealment, type of publication (full paper, abstract, unpublished), fixed effect modeling vs. random-effects modeling. All statistical tests were two-sided.

We examined the funnel plot for OS to estimate the effect of small study size (i.e. publication bias) [15].

Results

Description of studies

Search of electronic databases yielded 986 references; 19 of them were potentially relevant. Reasons for exclusion are detailed in Figure 1 [16–25]. We found one ongoing trial eligible for this review but no clinical data could be obtained. Seven trials (nine publications) that randomized 4073 patients, and were performed between 1993 and 2008, fulfilled inclusion criteria [26–34].

Type of patients

All trials included patients with aggressive lymphoma. In three trials only patients with DLBCL were included [26,27,34]. One trial included patients with any type of aggressive lymphoma between 1999 and 2002, and from 2002 to 2005 included only those with B cell aggressive lymphoma [28].

The median age of included patients ranged between 52 and 70 years (Table I). Two trials limited inclusion criteria to patients above 60 years [27,30].

Central review of pathology was performed in six trials [26–31]. Diagnosis was changed after pathology review in 2–13% of patients. Three trials excluded patients due to problems in the review of the pathology process (no pathology review, change in original diagnosis) [28,30,31] (Table I).

The rate of patients with stage 3–4 lymphoma ranged from 48% to 88% (median 56.5%). According to the IPI score 25–67% were at low risk (Table I).

Patients were excluded in all trials if they had marked impairment of cardiac, pulmonary, hepatic, or renal function. Five trials excluded patients with central nervous system involvement [26,27,29–31]. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 in three trials [26,27,29], and 0–3 in three trials [30,31,34]. Performance status was not reported in one trial [28].

Type of therapy

Chemotherapy: standard CHOP regimen was given in four trials. In two trials patients were randomized to receive CHOP regimen with etoposide (CHOEP) or CHOP [30,31]. In one trial chemotherapy consisted of epirubicin 70 mg/m^2, cyclophosphamide 1000 mg/m^2, vicristine 2 mg, and prednisone 60 mg (CEOP) [28].

Rituximab therapy was added to chemotherapy for all patients in two trials [26,27], and to 54% of patients in one trial [28].

Actual dose intensities and treatment intervals were not uniformly reported among trials and are described in Tables I and II.

The practice of the use of GCSF differed among trials as specified in Table II.

Study design

All included studies were randomized controlled trials. Two trials [30,31] had 2*2 factorial design

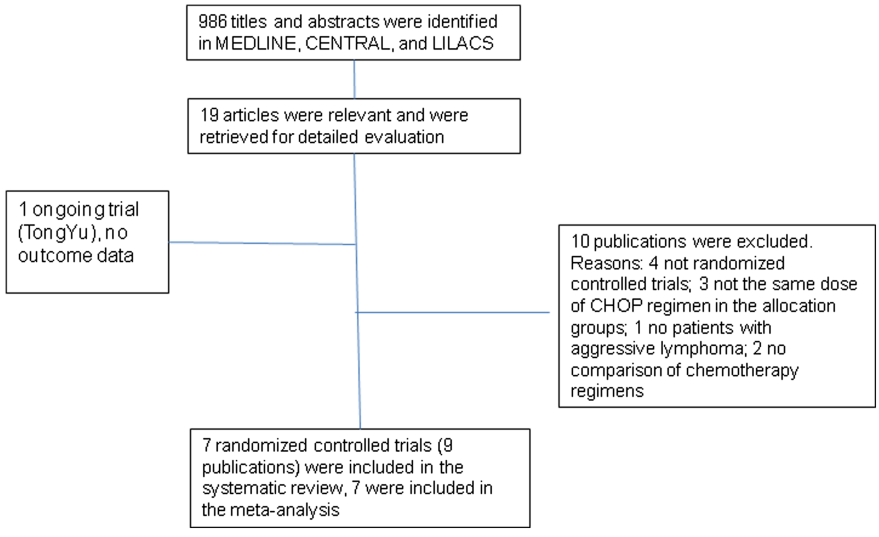

Figure 1. Flow diagram of inclusion of studies.

Table I. Characteristics of patients, and treatment, and risk of bias assessment of included trials.

	Cunningham	Delarue	Economopoulos	Omachi	Pfreundschuh/B1	Pfreundschuh/B2	Zhang
Number of randomized patients	1080	602	238	323	866	831	133
Age[years] restrictions	18 and older	66–80, modified to 60–80	No age limit	15–69	61–75	18–60	15–70
IPI > 1	70%	75%	54%	56%	33% aaIPI> = 1	71%	45%
Stage 3–4	62%	88%	49%	53%	61%	51%	47%
Number of cycles	R-CHOP-21* 8 R-CHOP-14* 6 + R*2	8	8	8	6	6	6–8
Allocation concealment	Adequate	Adequate	Not reported	Adequate	Adequate	Adequate	Not reported
Sequence generation	Adequate	Adequate	Not reported	Adequate	Adequate	Adequate	Not reported
Exclusions after randomization	0/1080 All patients were included in primary analysis	2/602 = 0.3% reasons and allocation were reported	21/238 = 9% due to pathology review process, allocation was not reported	All randomized patients were included in analysis of primary outcome	156/866 = 18% Data of allocation was obtained from investigators: 20% of CHOP-14, 16% of CHOP-21, reasons were specified for the cohort	142/831 = 17% Data of allocation was obtained from investigators: 20% of CHOP-14, 14% of CHOP-21, reasons were specified for the cohort	3/133 = 2% allocation was not reported

Table 2: Relative dose intensity and use of growth factors.

	Description of relative dose intensity	Use of growth factors	
		CHOP-14	CHOP-21
Cunningham	Among individuals who received eight planned treatment cycles (236 in the R-CHOP14 group and 234 in the R-CHOP-21 group), the median relative dose intensity for cyclophosphamide was 88% in the R-CHOP14 group and 97% in the R-CHOP21 group and for doxorubicin, median relative dose intensity was 88% and 96%, respectively. The same analysis was repeated for all patients who received the first four cycles, and the first two cycles of treatment and median relative dose intensities were similar.	100% of patients as part of the protocol	54% of patients
Delarue	The median ratio total dose achieved to planned and median dose intensities achieved to planned were about 98% in both groups, besides that of vincristine that was 77% in R-CHOP-21group.	90% of patients, decision of the treating physician	74% of patients, decision of the treating physician
Economopoulos	Median relative dose intensity of epirubicin, cyclophosphamide, rituximab in CEOP-14 were 1.12, 0.88, 0.78 and in CEOP-21 0.95, 0.93, 0.9, respectively. The definition of relative dose intensity was not reported in that trial.	Given to all patients according to protocol	At the desertion of the treating physician
Omachi	In the CHOP-21 group median relative doses of cyclophosphamide and doxorubicin were 97.2% and 99.4%, respectively, and in the CHOP-14 group 98.1% and 99.6%, respectively.	Given to all patients according to protocol	At the desertion of the treating physician
Pfreundchuh B1	Median relative dosage intensities for the myelosuppressive drugs cyclophosphamide, doxorubicin, and etoposide (in the case of the CHOEP regimens) were 98% for CHOP-21, 97% for CHOP-14 and CHOEP-21, and 95% for CHOEP-14.	96% (CHOP) and 100% (CHOEP)	6.0% (CHOP) and 16.9% (CHOEP)
Pfreundchuh B2	Median dose intensities for cyclophosphamide, doxorubicin, and vincristine were 97% for CHOP-21, 93% for CHOP-14, and 96% for CHOEP-21, and 83% for the CHOEP-14.	Growth factors were given to all patients in CHOP/CHOEP-14 group	
Zhang	Not reported.	Growth factors were used but unclear if given for all patients	

examining the effect of interval reduction and the addition of etoposide. In one trial two randomization procedures were taken: R-CHOP-14 or R-CHOP-21, and conventional management of chemotherapy-induced anemia or experimental arm with prophylactic darbepoetin alfa [26].

Risk of bias assessment (Table I)

Five trials were assessed as at low risk of selection bias (adequate allocation concealment and sequence generation) [26,27,29–31]. Two trials did not report methods of allocation generation and concealment and were judged at unclear risk of selection bias [28,34]. Rate of exclusion after randomization ranged from 0% to 18%. In two trials [30,31] the rate of exclusion after randomization was 17%, and 18%: in one trial of 866 randomized patients 6% had no pathology review, 7% diagnosis was changed on pathology review, 5% had protocol violation and were excluded. In one trial of 831 randomized patients 5.9% had no pathology review, 4.8% diagnosis was changed on pathology review, 6.4% protocol violation and were excluded.

Reasons for exclusion and allocation of excluded patients were reported in all but two trials [28,34].

Patients and caregivers were not blinded in all trials. Blinding of outcome assessors was not reported in all trials. One study was judged at high risk of reporting bias as OS was reported only for sub-group analysis and not for the whole cohort [34]. One trial was stopped earlier than planned due to lack of PFS benefit to avoid futility, therefore there is no support for overestimation of treatment effect in that trial [29].

Overall survival

Seven trials (3749 patients) were eligible for analysis of OS [26–31,34]. In one trial outcomes were reported as two different cohorts: patients with germinal center B cell (GCB) and non-GCB lymphoma [34]. Patients treated with CHOP-14 or CHOP-like-14 (with or without rituximab) had a statistically significantly improved OS compared to CHOP-21 or CHOP-like-21 (HR 0.86, 95% CI 0.77–0.97) (Figure 2). No statistical heterogeneity was observed for OS ($I^2 = 0$ and χ^2-tests). Examination of the funnel plot of OS did not support a publication bias.

Sub-group and sensitivity analyses. OS in the trials was analyzed separately according to the following variables:

Effect of the addition of rituximab: Patients treated with CHOP-14 or CHOP-like-14 (without rituximab) had a statistically significantly superior OS compared to the same regimen at 21 days interval (HR 0.82, 95% CI 0.70, 0.95, 4 trials, 1852 patients) [29–31,34]. The survival benefit was not shown in the subgroup of patients who received rituximab containing regimen (HR 0.93, 95% CI 0.78–1.10, 2 trials, 1680 patients) [26,27]. No statistically significant difference between these two sub-groups was demonstrated.

Supportive therapy: analysis of the five trials [26,28–31] in which prophylactic GCSF was given to all patients assigned to 14 days interval and at the discretion of the treating physician for those assigned to 21 days interval did not change the results (HR 0.85, 95% CI 0.75–0.98). Including only trials that compared

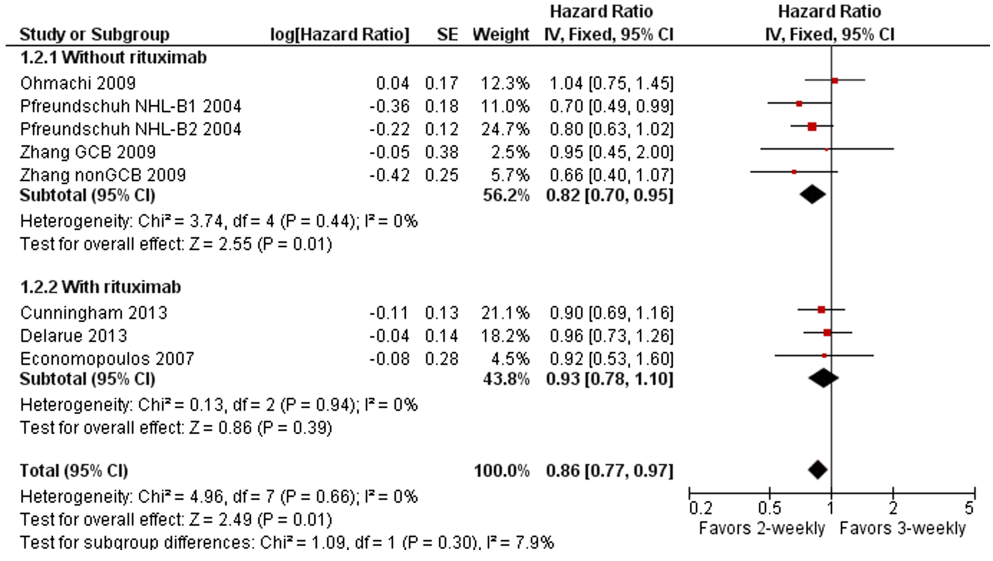

Figure 2. Pooled analysis of overall survival of patients treated with CHOP/CHOP-like 14 vs. CHOP/CHOP-like-21. Results are also shown in sub-group treated with rituximab containing therapy and without rituximab. CI, confidence interval; IV, inverse of variance; SE, standard error. Zhang 2009 reported survival as two separate cohorts (patients with GCB and non-GCB lymphoma) as represented in the figure.

CHOP-like-14 to CHOP-like-21 with rituximab in the majority of patients the HR of death was 0.90, 95% CI 0.71–1.13 [26,28].

Age of patients: In a sub-group meta-analysis of elderly patients (2002 patients, 4 trials [26,27,29,30]) HR of death was 0.91 with a 95% CI 0.79–1.06. Analysis of patients up to 60 years (1400 patients, 3 trials [26,29,31]) showed a HR of 0.79, 95% CI 0.63–1.00 suggesting a benefit for these patients with dose dense chemotherapy. Despite of the stated above it should be noted that no support of between sub-groups difference was shown.

Standard CHOP chemotherapy: Patients who received R-CHOP/CHOP-14 had an improved OS compared to R-CHOP/CHOP-21 (HR 0.84, 95% CI 0.74–0.97, 5 trials, 2483 patients) [26,27,29,30,34].

Type of lymphoma: patients with DLBCL treated with CHOP-14 or CHOP-like-14 (with or without rituximab) did not have a statistically significantly different OS compared to the same regimen at 21 days interval (HR 0.89, 95% CI 0.75–1.05, 3 trials, 1810 patients) [26,27,34]. Patients with any aggressive lymphoma (including DLBCL and T cell lymphoma) treated with CHOP-14 or CHOP-like-14 had an improved OS compared to the same regimen at 21-days interval (HR 0.83, 95% CI 0.70–0.98, 3 trials, 1722 patients) [29–31].

IPI risk category: only two trials [26,29] reported outcomes by the IPI risk category. No effect on OS of CHOP-14 compared to CHOP-21 was demonstrated in patients with low or low-intermediate risk categories (HR 0.87, 95% CI 0.67–1.13) or the high or high risk categories (HR 1.09, 95% CI 0.83–1.44).

Sensitivity analysis by the risk of bias: analysis of trials at low risk of selection bias showed that effect of 14 days interval was similar to that in the primary analysis (HR 0.87 95% CI 0.77–0.99) [26,27,29–31]. Analysis excluding two trials [30,31] with high attrition rates demonstrated that the estimate remained in favor of the 14 days interval but it was no longer statistically significant.

Secondary outcomes

There was no statistically significant difference in the pooled HR of progression or death (PFS) 1.00, 95% CI 0.86–1.15 (3 trials, 2003 patients) [26,27,29] between the 14 and 21 days regimens.

No statistically significant difference in the rate of complete response was shown with CHOP/CHOP-like-14 s. CHOP/CHOP-like-21 (HR 1.03 95% CI 0.98–1.07, 7 trials, 3671 patients, I^2 of heterogeneity = 61%).

Adverse events

No differences were observed in the risk of treatment related mortality (RR 1.14 95% CI 0.77, 1.70, 5 trials, 2885 patients) [26–29,31], grade 3 or 4 infection (RR 1.09, 95% CI 0.94–1.26, 7 trials, 3724 patients) [26–32,34], febrile neutropenia, and discontinuation of therapy due to an adverse event (RR 0.86, 95% CI 0.65–1.14, 4 trials, 2195 patients) [26–29]. Due to the different outcome reported (neutropenia, leukopenia), and different practice of GCSF use in the different trials that led to high statistical heterogeneity we did not perform a meta-analysis of grade 3 or 4 leukopenia or neutropenia. Relative risks of grade 3 or 4 leukopenia or neutropenia were in favor of CHOP-14 compared to CHOP-21 in 2 trials [26,28] and did not differ between the allocation groups in four trials [27,29–31].

Quality of life was not reported in any of the trials.

Discussion

CHOP or CHOP-like regimen was shown to improve OS when given every 14 days instead of 21 days. However, this effect was shown only in three subgroups: among patients younger than 60 years with borderline statistical significance ($p = 0.05$), among patients who were not treated with rituximab, and among patients who received standard CHOP regimen (excluding CHOP-like regimens). Conversely among patients treated with rituximab (R-CHOP), patients 60 years old and above, patients with DLBCL, and patients at any IPI category no effect of dose dense protocol was shown. Most included trials were at low risk of selection bias, and none of the trials was blinded.

To the best of our knowledge this is the first systematic review and meta-analysis assessing the effect of dose dense chemotherapy for patients with aggressive lymphoma.

Although not statistically significant, a between studies difference (heterogeneity) of the effect of the 14 days interval was noticed. Factors that may contribute to these differences may be different patient characteristics as a higher rate of patients in lower risk categories in one trial [30]; difference in rate of patients' exclusion after randomization; slight differences in supportive treatment; difference in lymphoma treatment (rituximab); and differences in adherence to the protocol. It also may implicate that such factors may interact with treatment effect with the effect of 14 days interval and there are subgroups that will benefit from dose dense while other sub-groups do not.

A subgroup analysis may reveal who benefits most from the dose dense chemotherapy, but by its nature such an analysis has a smaller sample size and a lesser

power to demonstrate effect. This may explain the lack of statistical significance in some of these analyses.

As the review included trials conducted prior to the inclusion of rituximab in the standard treatment of B cell aggressive lymphoma, patients were treated with CHOP without rituximab in some of the trials. As mentioned above with current standard of care, R-CHOP or R-CHOP-like regimen given every 14 days instead of 21 days no OS benefit was shown. Post-hoc exclusion of trials [27,34] in which prophylactic GCSF was not given to the CHOP-like-14 group did not affect the results of the whole group, nor that of the sub-group of patients treated with rituximab. It is unclear why the addition of rituximab to the dose dense CHOP regimen diminishes the OS advantage. It seems that the addition of rituximab to both regimens (standard 21 days interval and dose dense 14 day interval) equalizes their efficacy. One possibility is that the myelotoxicity which is higher in the dose dense regimen might interfere with the effector mechanism of rituximab, mainly the antibody-dependent cellular cytotoxicity, and this might reduce the therapeutic effect of rituximab when combined with dose dense regimens [28]. It is unclear whether there are sub-groups of patients treated with CHOP-rituximab that may benefit from decreasing the dose interval.

It should be noted that in the three trials that used R-CHOP protocol treatment was repeated for eight cycles. Six courses were found to be as least as good as eight cycles with a 14 days schedule in a randomized trial while such a study comparing 6–8 cycles has not been performed for CHOP-21 [35].

It is difficult to compare protocol adherence, treatment intervals, and dose intensity among trials as these were not uniformly reported. In most of the included trials there were no major differences between the two allocation groups. In one trial [27] in 16% of patients assigned to RCHOP-14 the median time between cycles was longer than 18 days. Once again a post-hoc analysis without that trial did not change the results.

We used a comprehensive search of available literature, including gray literature to reduce the possibility of publication bias. Examination of the forest plot of the primary outcome does not support a publication bias. We included controlled randomized trials to eliminate the risk of selection bias. We made efforts to contact all first or corresponding authors for complementary data. Using published and unpublished data we were able to include all seven trials in analysis of primary outcomes.

Some patients would consider 14 days schedule to be preferred to the 21 days schedule as six courses is finished at least six weeks earlier.

In conclusion, R-CHOP-21 or R-CHOP-like-21remains the standard of care for patients with B cell aggressive lymphoma.

As the risk of adverse events with CHOP-14 were not increased compared to CHOP-21 it might be considered in patients who cannot tolerate rituximab, for patients with T cell lymphoma, and at patient's preferences.

Individual patient meta-analysis may spread light on outcomes of these patients. Future randomized controlled trials of dose dense chemotherapy should focus on patients with T-cell lymphoma.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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