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Treatment of patients with diffuse large B-cell lymphoma

Leczenie chorych z chłoniakami rozlanymi z dużych komórek B

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Abstract

In the last 10 years, options for treating patients with diffuse large B-cell lymphoma (DLBCL) have greatly expanded. In randomized clinical studies, the addition of rituximab to cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP) delivered every 3 weeks (R-CHOP) has been associated with improved survival rates, without increased toxicity, in all patient groups studied. Another strategy, giving patients dose-dense CHOP — CHOP every 2 weeks or CHOP-14 — has also been found appropriate for all patients between the ages of 18 and 75 years but probably not superior to R-CHOP-21. Strategies with dose-intense regimens are currently tested for improving the outcome of young patients with poor risk DLBCL. In elderly patients, improvement in outcomes might be caused by the addition of another drug to the R-CHOP regimen. Elderly patients are best treated with R-CHOP if they do not have severe concomitant diseases.

Key words: non-Hodgkin lymphoma, diffuse large B-cell lymphoma, CHOP, rituximab, dose intensity, elderly

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Streszczenie

W ostatniej dekadzie odnotowano istotne zwiększenie możliwości terapeutycznych u chorych z chłoniakami rozlanymi z dużych komórek B (DLBCL). W randomizowanych badaniach klinicznych wykazano, że dodanie rytuksymabu do schematu cyklofosfamid, winkrystyna, doksorubicyna, prednizon (CHOP), stosowanego co 3 tygodnie (R-CHOP) przyczyniło się do wydłużenia czasu przeżycia wszystkich badanych grup chorych bez nasilenia toksyczności. Inna strategia, polegająca na skróceniu odstępu pomiędzy kolejnymi cyklami CHOP do 2 tygodni (CHOP-14), również wydaje się możliwa do zastosowania u wszystkich chorych w wieku 18–75 lat, ale prawdopodobnie nie jest bardziej skuteczna niż R-CHOP-21. Strategie zwiększające intensywność dawki są obecnie badane z intencją poprawy wyników leczenia u młodszych chorych z DLBCL o wysokim ryzyku. U chorych w starszym wieku poprawy wyników leczenia można się spodziewać po dołączeniu innych leków do schematu R-CHOP. W przypadku niewystępowania ciężkich chorób towarzyszących jest to wciąż zalecany schemat leczenia w tej grupie wiekowej.

Słowa kluczowe: chłoniaki nieziarnicze, chłoniak rozlany z dużych komórek B, CHOP, rytuksymab, intensywność dawki, podeszły wiek

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Introduction

Non-Hodgkin lymphoma (NHL) remains a substantial contributor to the incidence of and mortality associated with cancer in Europe. European cancer registry data suggest that the incidence of NHL had been increasing till the mid-1990s, and then began to plateau [1–3]. In 2006, an estimated 72,800 new cases were diagnosed, up from 62,300 in 2004 [4, 5]. Non-Hodgkin lymphoma accounted for 3.2% of new cancer cases, 2.8% of all cancer deaths, and became the eighth leading cause of new cancer cases and the tenth leading cause of cancer deaths in Europe in 2006 [4].

The most common form of NHL is diffuse large B-cell lymphoma (DLBCL), which accounts for 30% to 35% of NHL cases [6]. The incidence of DLBCL increases with advancing age, such that the disease represents 54% of NHL cases among patients older than 75 years [7]. For nearly 3 decades, the standard of care for patients with DLBCL was cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP), which was established in 1976 as a regimen that induced high rates of overall response and complete remission in patients with advanced NHL [8]. CHOP was later proved to be superior to more complicated regimens in respect to the cost and severity of toxicity, and equally effective in terms of disease-free and overall survival rates [9]. Still, the cure rate with CHOP was suboptimal, with 10-year progression-free survival (PFS) and overall survival (OS) rates by approximately 30% and 35%, respectively [9].

An important limitation of the reported data was that physicians were circumspect in treating people over 60 years of age, who constitute more than 50% of patients with aggressive NHL [10]. Even after CHOP was established as the standard of care, many older patients with DLBCL were treated without doxorubicin, or treatment was completely withheld because of concerns about cardiotoxicity and other potential side effects. According to the analysis of a Dutch population-based NHL registry between 1981 and 1989, that studied CHOP in patients with DLBCL stratified into 5 age groups (< 60, 60–64, 65–69, 70–74, and > 75 y) , rates of complete response (CR) progressively declined after age 65, and relative 5-year OS progressively declined after age 60 [7].

This manuscript reviews studies of three strategies that have been proven to improve outcomes for patients with DLBCL by the addition of rituximab to CHOP (R-CHOP), dose intensification of CHOP, by either dose escalation or densification, and using R-CHOP in elderly patients.

How to stratify patients with DLBCL?

The International Prognostic Index (IPI) was described more than 15 years ago and remains the best prognostic indicator for patients with DLBCL, as shown in Figure 1 [10]. In this study, all DLBCL patients, who have entered randomized studies

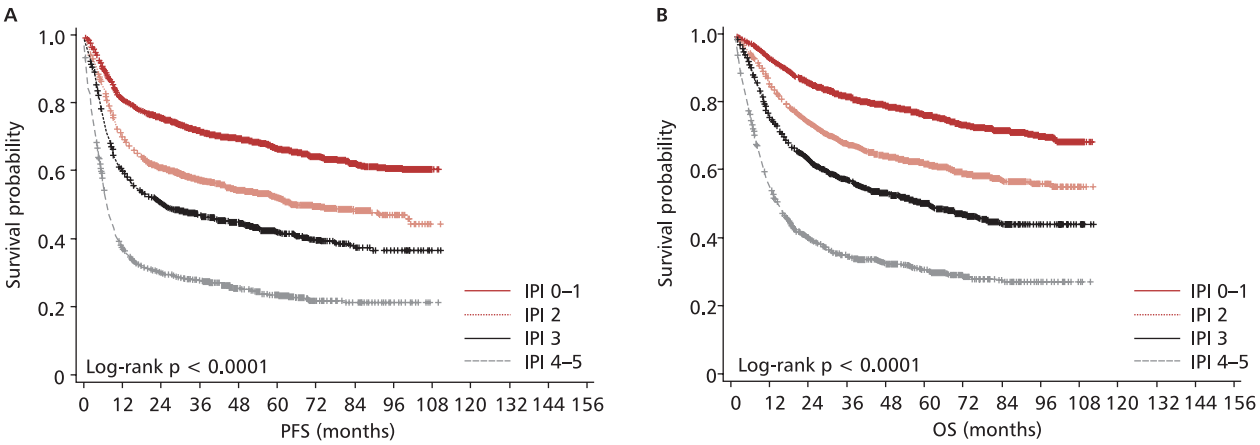


Figure 1. Survival in 6696 patients included in the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) randomized studies for whom all parameters of the International Prognostic Index (IPI) were present at diagnosis. **A.** Progression-free survival (PFS); **B.** Overall survival (OS)

Rycina 1. Przeżycie 6696 chorych przydzielonych metodą randomizacji do badań *Groupe d'Etude des Lymphomes de l'Adulte* (GELA), dla których wszystkie parametry wchodzące w skład Międzynarodowego Indeksu Rokowniczego (IPI) były znane w chwili rozpoznania. **A.** Czas do progresji choroby (PFS); **B.** Całkowity czas przeżycia (OS)

from the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA), and who had parameters to calculate the IPI at diagnosis were analyzed. It clearly showed the difference according to the number of adverse prognostic parameters present at diagnosis. Since then, numerous studies have tried to describe a better index with the addition of biological or genetic parameters, but with no success. This was mainly due to the fact that the new parameters were not standardized and have not been analyzed in large prospective studies [11].

Increased age is associated with the presence of concommitant diseases. It also decreases the ability of patients to tolerate treatments, and thus, physicians have a tendency to decrease the intensity of chemotherapy in these patients [12]. It results in poorer outcomes in elderly patients [13]. Patiens are stratified according to age taken as a putative index of treatment feasibiliy. In 1980's, 60 years was considered as the threshold for elderly patients. This threshold was considered as the limit for patients entering a study with higher dose regimens or autologous transplant in first line. Although patients aged 65 can probably tolerate higher dose regimens, they are at risk for more pronounced complications. Another threshold was recently described for very old patients, older than 80 years of age. These patients have usually several concommitant diseases that decrease their ability to tolerate the R-CHOP regimen [14].

Evolution of R-CHOP as the standard of care

Rituximab is a human-murine IgG1 monoclonal antibody against the B-cell surface antigen CD20, which is routinely expressed in patients with DLBCL and other B-cell lymphomas. The first randomized study of a rituximab-chemotherapy combination in lymphoma was the LNH98-5 trial of GELA which compared R-CHOP with CHOP in older patients (60–80 y) with DLBCL [15–17]. With a median follow-up of 2 years, then 5 and 10 years, the results showed that R-CHOP significantly increases the CR rate, improved event-free survival (EFS), disease-free survival and overall survival (OS), and strongly decreased the rates of treatment failure and relapse, compared with standard CHOP alone (Figure 2). These improvements occurred in patients ≥ 70 years old and in those with scores of 2 or 3 on the age-adjusted International Prognostic Index (aaIPI), as well as in lower-risk patients, and there was no clinically significant increase in toxicity. Table 1 provides further details of this trial and the other studies discussed in this section.

Longer-term analysis of GELA LNH98-5 showed that the survival benefits extended to up to 7 years, and no long-term toxicity was associated with R-CHOP [18]. These longer survival rates in the R-CHOP group were secondary to the lower rate of disease progression during therapy and fewer

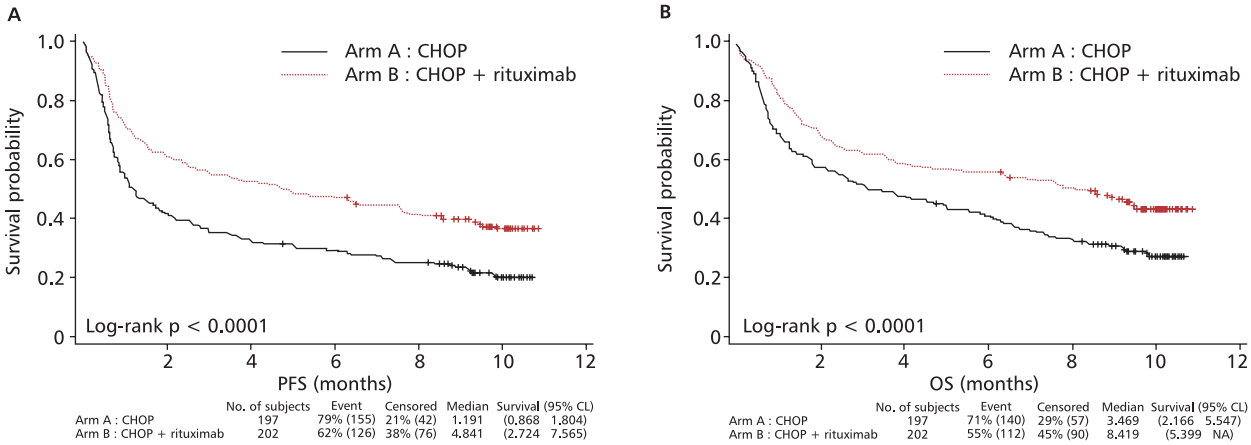


Figure 2. 10-year follow-up of the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) study comparing cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP) to rituximab-CHOP [17] **A.** Progression-free survival (PFS); **B.** Overall survival (OS)

Rycina 2. Dziesięcioletni okres obserwacji wyników badania *Groupe d'Etude des Lymphomes de l'Adulte* (GELA), w którym porównano stosowanie schematu cyklofosfamid, winkrystyna, doksorubicyna, prednizon (CHOP) ze schematem CHOP w połączeniu z rytuksymabem [17]. **A.** Czas do progresji choroby (PFS); **B.** Całkowity czas przeżycia (OS)

Table 1. Comparisons of cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP) *vs.* rituximab-CHOP (R-CHOP)

Tabela 1. Porównanie schematu cyklofosfamid, winkrystyna, doksorubicyna, prednizon (CHOP) ze schematem CHOP w połączeniu z rytuksymabem (R-CHOP)

Study	Population	Design*	Primary outcome measure(s) (95% CI)	Safety results
GELA LNH98-5 (Coiffier et al., 2002)	399 patients with untreated DLBCL, age 60–80 y	Random assignment to 8 cycles of CHOP or R-CHOP	2-y EFS: CHOP: 38% (32–45%) R-CHOP: 57% (50–64%) p < 0.001	No significant difference between groups in clinically relevant toxicity
Longer-term analysis of GELA LNH98-5 (Feugier et al., 2005)	As above	As above	5-y EFS: CHOP: 29% (23–36%) R-CHOP: 47% (40–54%) p = 0.00002	No long-term toxicity appeared to be associated with R-CHOP
US Intergroup trial (Habermann et al., 2005)	632 patients with untreated DLBCL, age ≥ 60 y	Random assignment to CHOP or R-CHOP (6 or 8 cycles, depending on response after 4 cycles; R was administered 7 and 3 days before cycle 1, and 2 days before cycles 3, 5, and 7) 415 responders to CHOP or R-CHOP were randomly assigned to observation or maintenance R (4 courses at 6-mo intervals)	3-y FFS after induction therapy: CHOP: 46% R-CHOP: 53% HR = 0.78 (0.61–0.99); p = 0.04 Estimated 2-y FFS after second random assignment: maintenance R: 76% observation: 61% HR = 0.63 (0.44–0.90); p = 0.009	Not reported
Canadian population-based analysis (Sehn et al., 2005)	292 patients with advanced DLBCL, median age 64 y (range, 19–86 y)	Retrospective database analysis comparing 140 patients treated with CHOP-like chemotherapy (median follow-up 42 mo) and 152 patients treated with CHOP-like chemotherapy + R (median follow-up 24 mo)	2-y PFS: without R: 51% with R: 69% RR = 0.56 (0.39–0.81); p = 0.002 2-y OS: without R: 52% with R: 78% RR = 0.40 (0.27–0.61); p < 0.0001	Not reported
MInT (Pfreundschuh et al., 2006a)	326 patients†, age 18–60 y, with good-prognosis untreated DLBCL (aaIPI = 0–1 in stage II–IV disease, or stage I disease with bulk)	Random assignment to 6 cycles of CHOP-like chemotherapy alone or with R	Estimated 3-y EFS: without R: 68% (62–73%) with R: 85% (81–89%) p < 0.0001	No significant difference between groups in frequency of adverse events
DSHNHL RICOVER-60 (Pfreundschuh et al., 2006c)	1222 patients, age 61–80 y, with DLBCL	Random assignment with DLBCL to 6 or 8 cycles of CHOP-14, with or without R (regardless of the number of cycles, 8 R infusions were given)	Estimated 3-y EFS: 6 × CHOP-14: 47% 8 × CHOP-14: 53% 6 × R-CHOP-14: 66% 8 × R-CHOP-14: 63% EFS compared with 6 × CHOP-14†: 8 × CHOP-14: RR = 0.76; p = 0.017 6 × R-CHOP-14: RR = 0.51; p < 0.001 8 × R-CHOP-14: RR = 0.54; p < 0.001	Not reported
HOVON (Sonneveld et al., 2006)	243 patients* , age ≥ 65 y, with untreated intermediate- or high-risk B-cell NHL	8 cycles of CHOP-14 with random assignment to receive or not receive 6 infusions of R (G-CSF support in both arms)	Estimated 2-y FFS: CHOP-14: 33% R-CHOP-14: 55% HR = 0.60; p = 0.007	64% of patients completed planned treatment; 22% of patients went off treatment due to toxicity; 15% of patients < 70 y went off treatment due to toxicity

*Regimens were given at standard doses unless specified otherwise; †trial was stopped prematurely; 824 patients were enrolled; aaIPI — age-adjusted International Prognostic Index; CI — confidence interval; DLBCL — diffuse large B-cell lymphoma; EFS — event-free survival; FFS — failure free survival; GELA — *Groupe d'Etude des Lymphomes de l'Adulte*; HR — hazard ratio; MInT — MabTher International Trial; mo — months; OS — overall survival; PFS — progression-free survival; R — rituximab; RR — risk ratio; y — year(s)

relapses among patients who had CR; this effect was still evident at 10 years of follow up [17].

The US Intergroup study also compared R-CHOP and CHOP in older patients (≥ 60 y) [19]. The double blind, randomized trial addressed the two major types of treatment failure in aggressive NHL: the failure of induction therapy and failure to maintain CR [20]. Patients were initially assigned to the R-CHOP or CHOP group, and responders received either no additional treatment or maintenance of rituximab for 2 years. Regardless whether rituximab was part of induction therapy or maintenance after CHOP, it significantly improved failure-free survival (FFS, the time from random assignment to relapse, non-protocol treatment, or death). The rituximab continuing use after R-CHOP was not shown to be beneficial.

After the 2-year results of GELA LNH98-5 were published, the British Columbia Cancer Agency recommended R-CHOP for all newly diagnosed patients with advanced DLBCL, regardless of age [21]. Investigators then retrospectively analyzed the outcomes of such patients during a 3-year period, 18 months before and after the policy was implemented. Regardless of patient age and treatment, both PFS and OS were significantly better in patients treated after the recommendation of R--CHOP than in those treated before (with CHOP alone), even after the investigators controlled for age and IPI score. Although the follow up length in the two study groups was different, this study remains very important because it reflects "real life" and there is no selection bias.

The benefits of R-CHOP also extend to younger adults with DLBCL who have a good prognosis. The MabThera International Trial (MInT), designed by cooperative groups from 18 countries, was stopped early when it demonstrated the superiority of R-CHOP over CHOP in that patient population [22]. At median follow-up of 34 months, EFS, PFS, and OS were significantly better in patients who received rituximab plus CHOP or CHOP-like chemotherapy than in those who received only chemotherapy. Only 21% of patients failed after chemotherapy plus rituximab, compared with 41% who failed after chemotherapy alone, suggesting that the proportion of young patients who need salvage treatment could be halved with rituximab. CHOEP (CHOP plus etoposide) was superior to CHOP with regard to EFS, but the comparison of R-CHOP and R-CHOEP showed no significant difference in EFS or overall survival. R-CHOP is therefore preferable to R-CHOEP because it has fewer toxic effects.

Thus, the addition of rituximab to CHOP has been associated with improvements in OS and in EFS or PFS, without increased toxicity, in all studied patient groups. The addition of rituximab to CHOP is now considered the standard of care for treatment of DLBCL with curative intent [23]. However, no study has addressed the group of young patients with adverse prognostic factors. R-CHOP was considered the standard of care, but it was not demonstrated to allow the same improvement in terms of survival. In the past, before rituximab era, it was demonstrated that some regimens with higher doses of doxorubicin and cyclophosphamide or with consolidation in first CR with high-dose therapy and autotransplant were better than CHOP for this purpose. At present time, we do not have definitive answers about rituximab. Several ongoing studies examine this subject but none has currently been presented. The GELA has released the interim analysis of the LNH03-2B study comparing R-CHOP to rituximab combined with the ACVBP regimen, a high-dose CHOP-like regimen to be superior to CHOP in some subgroups of DLBCL patients (Figure 3) [24]. This interim analysis with 185 of the 380 randomized patients shows an identical CR rate between the two regimens but a longer not yet statistically significant EFS and a significantly longer DFS ($p = 0.024$) for patients treated

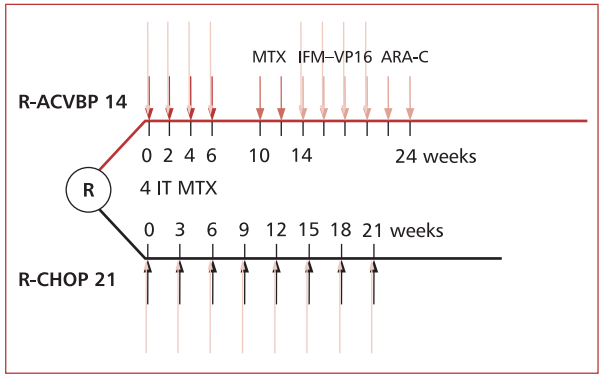


Figure 3. Design of the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) study comparing R-CHOP-21 to R-ACVBP. This study has acrued 380 patients with a primary endpoint of event-free survival

Rycina 3. Założenia badania *Groupe d'Etude des Lymphomes de l'Adulte* (GELA), porównującego stosowanie schematu R-CHOP-21 ze schematem R-ACVBP. Do badania z pierwszorzędowym punktem końcowym w oparciu o czas wolny od zdarzeń zrekrutowano 380 chorych

with R-ACVBP. If these results are confirmed with longer follow-up, it will open the case for moving to "intensive" R-CHOP for young patients with adverse outcomes.

Patients with localized disease

Classically, these patients were treated with 3 cycles of CHOP followed by radiation therapy, but definitive data proving that this was the best treatment are unavailable. Two randomized studies were run by the GELA comparing chemotherapy with or without radiation therapy and did not show any benefit in favor of radiation therapy. The first study in young patients with disease stage I or II compared 3 cycles of CHOP plus radiation therapy to ACVBP regimen (with only 3 cycles of high-dose CHOP). Patients treated with ACVBP had longer EFS and OS [25]. In the second study, elderly patients with disease stage I or II DLBCL were randomized between 4 cycles of CHOP or 4 cycles of CHOP plus radiation therapy (Figure 4). EFS and OS were identical in both arms with more secondary cancer with radiation therapy [26]. The results were inferior to what may be expected in good risk patients, allowing the conclusion that 4 cycles of CHOP is insufficient for some of these patients.

In rituximab era, a lot of these patients were treated with 4 cycles of R-CHOP with or without radiation therapy. However, 4 cycles of R-CHOP is probably sufficient to cure a majority of these patients if they respond rapidly with a non-fixing PET scan [27]. A subgroup of them with persisting disease represents refractory patients who require a more intense regimen.

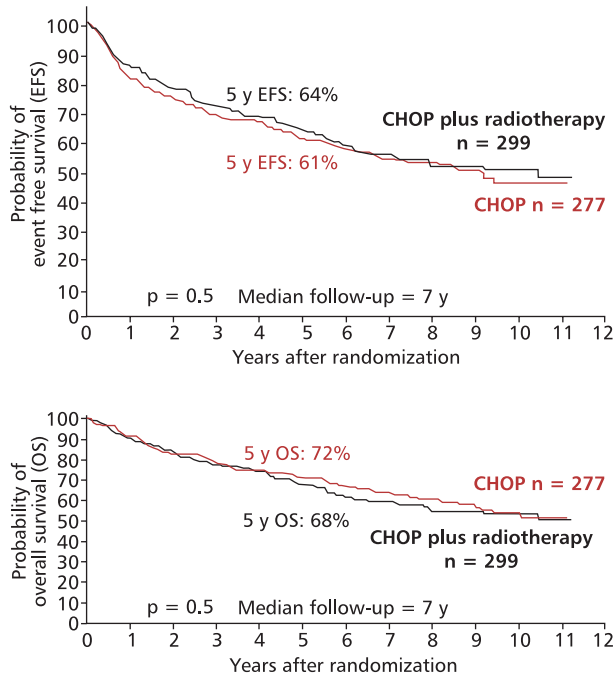


Figure 4. *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) study comparing cyclophosphamide, vincristine, doxorubicin, prednisone (CHOP) to CHOP plus radiation therapy in elderly patients with localized diffuse large B-cell lymphoma (DLBCL) and International Prognostic Index (IPI) score = 0 [26]

Rycina 4. Badanie *Groupe d'Etude des Lymphomes de l'Adulte* (GELA), w którym porównano stosowanie schematu cyklofosfamid, winkrystyna, doksorubicyna, prednizon (CHOP) bez radioterapii oraz w skojarzeniu z radioterapią u osób w podeszłym wieku ze zlokalizowaną postacią chłoniaka rozlanego z dużych komórek B (DLBCL) oraz z Międzynarodowym Indeksem Prognostycznym (IPI) = 0 [26]

Dose densification of CHOP and CHOP-like regimens

Concurrently with the studies of rituximab, investigators have been examining whether they might improve outcomes in patients with aggressive lymphoma by increasing the chemotherapy dose intensity (the amount of drug delivered per unit of time). Dose intensification can be accomplished through dose escalation (increasing the amount of drug given per cycle) or dose densification (reducing the time between treatment cycles).

Several studies have tried to improve results by modifying the doses given at each cycle or shortening the schedule. The German group (GLSG) has presented several studies with shortening the interval between cycles from 21 days to 14 days (CHOP-14) without changing the dose of the regimen without, then with rituximab. The first set of studies compared CHOP-14 to CHOP-21, with or without etoposide, in young or elderly patients [28, 29]. Theses studies concluded that CHOP-14 was superior to CHOP-21 in elderly patients but not in young patients. The addition of etoposide improved outcomes in young patients but not in elderly ones.

Thereafter, the same group has tested the benefit of the addition of rituximab to CHOP-14 (RICOVER study) [30]. They also tested the number of cycles of chemotherapy (6 or 8), all patients randomized to rituximab receiving 8 infusions. Using 6 cycles of CHOP-14 (6 × CHOP-14) as the comparator, EFS was significantly better in both rituximab arms (Table 2), but OS was significantly better only with 6 × R-CHOP-14. However, outside Germany, most physicians consider that the benefit of R-CHOP-14 is not proven and it is

Table 2. Studies with CHOP-14 with or without rituximab

Tabela 2. Badania CHOP-14 z lub bez rytuksymabu

Study	Design	Regimens	Number of patients	Conclusion on EFS or PFS	Conclusion on OS	Conclusion on safety
NHL-B1 [28]	Randomized study in young patients (double randomization)	CHOP-14 *vs.* CHOEP-14 *vs.* CHOP-21 *vs.* CHOEP-21	172 177 176 185	No improvement for CHOP(E)P-14 Improvement for CHOEP (p = 0.004)	Trend for improvement of EFS (p = 0.05) No improvement for CHOEP	G-CSF mandatory for CHO(E) P-14 More hematological toxicity with CHOEP-14
NHL-B2 [29]	Randomized study in elderly patients (double randomization)	CHOP-14 *vs.* CHOEP-14 *vs.* CHOP-21 *vs.* CHOEP-21	172 169 178 169	CHOP-14 reduced the risk of an event. No difference for the addition of etoposide	CHOP-14 reduced the risk of dying from lymphoma. No improvement for the addition of etoposide	G-CSF mandatory for CHO(E)P-14. More hematological toxicity for etoposide and CHOP-14
Halaas [55]	Retrospective analysis	R-CHOP-14	49	Short follow-up (2 y). Good risk patients. No real data to evaluate the efficacy		Hematology and neurological toxicity
Brusamolino [56]	Phase II	R-CHOP-14	50	2-year EFS and OS inferior to the one observe in the previous report (68% and 72%, respectively)		More infection than expected (*Pneumocystis carinii*)
Wolf [57]	Phase II	CHOP-14	30	Nothing in outcome		Hematologic toxicity
Kolstad [58]	Retrospective analysis	R-CHOEP-14	46	Nothing in outcome		6 cases of *pneumocystis carinii* infection
Mey [59]	Phase II	R-CHOP-14	10	Evaluation of Pegfilgastrim		Grade 3/4 neutropenia in all patients
Rueda [60]	Phase II in patients < 70 y	R-CHOP-14	80	25% progression with a median follow-up of 2 years		Well tolerated; *mucositis*; 19% hospitalizations
RICOVER-60 [30]	Randomized study, elderly patients	CHOP-14 *vs.* R-CHOP-14 6 *vs.* 8 cycles	1222	R-CHOP-14 improved EFS. No difference between 6 and 8 cycles	R-CHOP-14 improved OS. No difference between 6 and 8 cycles	More toxic events with 8 cycles
Cunnigham [33]	Randomized study	R-CHOP-14 *vs.* R-CHOP-21	1080	Interim analysis. Short follow-up (< 2 y). No difference between the 2 arms		More toxicity without G-CSF
Delarue [34]	Randomized study, elderly patients	R-CHOP-14 *vs.* R-CHOP-21	600	Interim analysis. Short follow-up (< 2 y). No difference between the 2 arms		Slightly increased toxicity for C-CHOP-14 patients

EFS — event free survival; OS — overall survival; PFS — progression-free survival; NHL — non-Hodgkin lymphoma; CHOP — cyclophosphamide, vincristine, doxorubicin, prednisone; CHOEP — cyclophosphamide, vincristine, doxorubicin, etoposide, prednisone; R — rituximab; G-CSF — granulocyte colony-stimulating factor; y — year(s)

more toxic than standard R-CHOP-21. Two randomized studies are currently looking at R-CHOP every 2 weeks, but until their results become available R-CHOP-21 will remain the standard of care.

A subgroup analysis of the RICOVER-60 data showed no difference in efficacy between 6 and 8 cycles of therapy in patients with either good or poor prognosis [31]. In contrast, in both subgroups, TTF was significantly better with R-CHOP-14 than with CHOP-14. Before and after rituximab infusion during each cycle in RICOVER-60, blood samples were taken from 18 participants in the R-CHOP-14 arm. According to pharmacokinetic analysis, rituximab levels reached their nadir after the first cycle of R-CHOP-14, then increased after each subsequent cycle. The researchers speculate that the nadir would be even lower in an every-3-week schedule of R-CHOP. Thus, as the researchers note, it appears that dose-dense rituximab (given every 2 weeks), not just dose-dense CHOP, contributed to the excellent results of the RICOVER-60 trial. The DSHNHL investigated dose-dense rituximab in combination with CHOP-14 in an ongoing phase 1 and 2 study, and the early results are encouraging.

Somewhat similar to RICOVER-60, a study conducted by HOVON and the Nordic Lymphoma Group compared CHOP-14 and R-CHOP-14 (both arms with G-CSF support) in older patients, age > 65 years [32]. This trial was stopped early because the addition of rituximab to CHOP-14 significantly improved the primary outcomes. As shown in Table 2, the results were not as impressive as those of RICOVER-60, but are encouraging owing to the fact that > 60% of these older patients, with a median age of 72 years, tolerated the regimen.

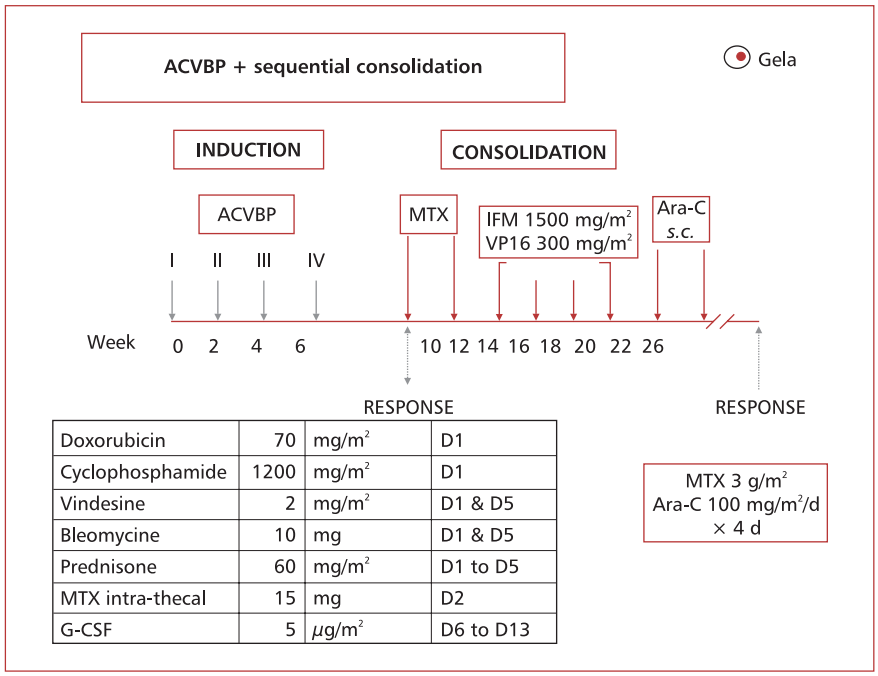
Since the addition of rituximab to CHOP (R-CHOP-21) is standard in most countries and CHOP-14 has been shown to be effective, a key research question is whether the addition of rituximab to CHOP-14 (R-CHOP-14) produces further benefits when compared to R-CHOP-21. Two ongoing trials are addressing this issue by comparing R-CHOP-21 with R-CHOP-14. A multicenter randomized trial headquartered at University College London is making this comparison in young and old patients with untreated DLBCL. An interim analysis was presented this year at the ASCO meeting [33]. No difference in term of CR rates and PFS were observed during a short follow-up. G-CSF was mandatory in the R-CHOP-14 arm and was not in the R-CHOP-21 arm, and it was not a surprise to see more neutropenia, febrile neutropenia, and infections in the later arm. In GELA LNH03-6B, patients between 60 and 80 years old, who had DLBCL and an aaIPI score ≥ 1, were randomly assigned to 8 cycles of R-CHOP-21 or R-CHOP-14 [34]. This interim analysis showed an identical response rate and a non-statistically significant difference in favor of R-CHOP-21 for EFS; the survival being identical. R-CHOP-14 patients were more likely to have more infections, mucositis, and needed more hospitalizations.

Thus, two interim analyses did not show any difference between R-CHOP-14 and R-CHOP-21. It is highly improbable that the complete analyses with a longer follow-up will show this difference. We may conclude that both regimens are equivalent for patients with DLBCL.

Dose intensification of R-CHOP

Patients with DLBCL whose IPI scores indicate they are at high-intermediate or high risk have less than 50% chance of being cured with R-CHOP [35]. Even in the MInT study of younger adults with a good prognosis, the outcomes varied among those who received rituximab plus CHOP-like chemotherapy: In the less favorable group (bulky disease, age-adjusted IPI [aaIPI] = 1, or both), 3-year EFS with rituximab was 78%, compared to 97% in the more favorable group (aaIPI = 0, no bulky disease) [22, 36]. Because the addition of rituximab to CHOP has become the standard of care for DLBCL, investigators are examining the effects of administering higher doses of chemotherapy agents, higher dose of rituximab or combining another drug to R-CHOP.

Before and after rituximab infusion during each cycle in RICOVER-60, blood samples were taken from 18 participants in the R-CHOP-14 arm. According to pharmacokinetic analysis, rituximab levels reached their nadir after the first cycle of R-CHOP--14, then increased after each subsequent cycle. Therefore the DSHNHL investigated dose-dense rituximab in combination with CHOP-14 in an ongoing phase 1 and 2 study, and the early results are encouraging [37]. In this study, rituximab was administered every week for the first 2 cycles and pharmacokinetics data confirmed the disappearance of this nadir. A randomized study is ongoing to test the hypothesis that higher blood level of rituximab is associated with higher response rate and PFS. Recently, it was demonstrated in mice studies that the tumor volume influenced the pharmacokinetic of rituximab and response to treatment [38]. The authors hypothesized that higher doses of rituximab would increase the efficacy of such therapy. This hypothesis is being currently tested in patients with DLBCL.



Doxorubicin	70	mg/m²	D1
Cyclophosphamide	1200	mg/m²	D1
Vindesine	2	mg/m²	D1 & D5
Bleomycine	10	mg	D1 & D5
Prednisone	60	mg/m²	D1 to D5
MTX intra-thecal	15	mg	D2
G-CSF	5	μg/m²	D6 to D13

Figure 5. ACVBP regimen used within the different *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) studies since 1984 [24, 61–63]

Rycina 5. Schemat ACVBP stosowany w różnych badaniach *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) od 1984 roku [24, 61–63]

The other way to increase the intensity dose is to increase the dose of CHOP or CHOP-like regimens. The DSHNHL conducted a randomized study to compare R-CHOEP-14 with a dose-escalated version in younger patients with aggressive NHL and a good prognosis [39]. The dose-escalated regimen (Mega-CHOEP) comprised cyclophosphamide 1400 mg/m^2, doxorubicin 65 mg/m^2, vincristine 2 mg, etoposide 175 mg/m^2 for 3 cycles (× 3), and prednisone 100 mg × 5. Mega-CHOEP was more toxic than standard treatment, and there was no difference in the time to treatment failure (TTF, the primary endpoint) or OS. Neither the low-risk nor the low-intermediate-risk subgroup benefited from the dose escalation. The cause of these unexpected results is not known.

However, the GELA has tested the combination of rituximab to its high-dose CHOP, ACVBP regimen (Figure 5), and has found to be superior to R-CHOP in two studies. The first study was a phase II study of R-ACVBP followed by autologous transplant in first CR in young patients with high risk DLBCL [40]. EFS was above 75% at 3 years. These results were compared with historical results in the same group of patients with the same treatment design, but without rituximab. The results showed 15% improvement in EFS demonstrating very good results with R-ACVBP in a subgroup of patients with high risk DLBCL. Another study compared the standard R-CHOP with R-ACVBP followed by sequential consolidation. In the interim analysis, there was a trend in favor of R-ACVBP for PFS. Final analysis of this study will be performed next year.

The last possible improvement could be the addition of another drug to R-CHOP. The addition of etoposide was tested by the German group: in elderly patients, R-CHOEP was more toxic but in young patients it seemed to be associated with good overall activity. Other targeted drugs are currently being tested, but no data have been made available yet: bevacizumab in a study comparing RA--CHOP to R-CHOP; lenalidomide in the R2-CHOP; or enzastaurin.

The conclusion of the discussed study is as follows: the standard R-CHOP is not sufficient in a subgroup of patients with high score IPI. However, because of the unavailability of the currently tested hypotheses, it is difficult to propose a 'standard' regimen for these patients.

Maintaining planned dose intensity

CHOP-based therapy has a number of dose-limiting toxicities, such as chemotherapy-induced neutropenia, particularly in older patients. In the NHL-B2 trial, the most common grade 3 or 4 toxicity was leukocytopenia, which occurred in 72% of patients who received CHOP-21, and in 70% of those who were treated with CHOP-14 [29]. Grade 3 or 4 thrombocytopenia occurred in 8% and 15% of patients, respectively, and grade 3 or 4 anemia affected 13% and 20%, respectively. Along with alopecia and nausea or vomiting, common non-hematologic grade 3 or 4 toxicities included infection, cardiac toxicity, neurological toxicity, lung toxicity, and, in the CHOP-14 arm, mucositis.

If CHOP side effects require dose reductions, dose delays, or chemotherapy withdrawal, patient survival can be negatively affected by the reduction in relative dose intensity (RDI, the proportion of the intended chemotherapy dose that a patient receives during a specified time period). In Belgium and the United Kingdom, audits of 289 NHL patients receiving CHOP-21 showed that 5-year OS was significantly associated with RDI ≤ 90% (hazard ratio,1.8; 95% confidence interval [CI], 1.1–2.8) [41]. These observations confirm earlier reports of associations between reduced RDI and reduced OS in patients with NHL [42–44].

Research conducted in routine community practice has documented that febrile neutropenia (FN) is a common cause of reduced RDI in patients with NHL. In Western Europe, a prospective observational study by Pettengell et al. [45] examined the impact of FN on chemotherapy in 34 centers. Of 240 patients with NHL, most received CHOP-like-21 (74%) or CHOP-like-14 (17%) chemotherapy. FN occurrence was ≥ 20% with CHOP-like-21 and most other NHL regimens. For patients with NHL the mean RDI was only 86%, and 32% of patients had low RDI (≤ 85%). Other risk factors for low RDI were advancing age, Eastern Cooperative Oncology Group performance status ≥ 2, fewer cycles of CSF administration, and first-cycle FN.

Pettengell [45] conclude that routine European practice should be revised to include primary prophylaxis with G-CSF if the patient will receive a chemotherapy regimen associated with an FN incidence ≥ 20% or is expected to receive less than optimal RDI. This recommendation echoes the recently published guidelines of the European Organization for Research and Treatment of Cancer (EORTC), which conclude that there is a strong and consistent evidence that G-CSF prophylaxis can maintain chemotherapy at the desired dose, intensity or density and minimize delays [46].

The future of therapy for aggressive NHL

The success of rituximab in the treatment of aggressive NHL has prompted the investigation of monoclonal antibodies that target other surface proteins and antigens commonly expressed in B-cell lymphoma. The most promising are antibodies against CD40, B-cell–activating factor of the TNF family (BAFF), and receptors for TRAIL (TNF-α-related apoptosis-inducing ligand, also known as Apo2L) [47]. Another approach is to use small molecules to target intracellular pathways that have a role in tumor cell survival and growth. For example, a multicenter phase 2 study using bortezomib, a protease inhibitor, in patients with relapsed or refractory mantle cell lymphoma, showed that it provided substantial activity in terms of durable and complete response, with predictable and manageable toxicity [48]. Although the effort is largely theoretical at this time, it may also be possible to identify small molecules to target certain classes of mitotic kinases that regulate cell division and mitosis. Lenalidomide, an agent with mechanisms of action that differ from chemotherapy or monoclonal antibodies, has activity in lymphoma and may be combined with R-CHOP to improve response rate or decrease relapse rate [49–53]. Finally, researchers are combining bevacizumab or thalidomide with rituximab, CHOP, or R-CHOP to determine whether it might be worthwhile to target tumor angiogenesis in NHL [54]. Although most of these agents and regimens are still in early development, it seems likely that at least a few more targeted therapies for NHL will soon be available.

Conclusion

The addition of rituximab to CHOP and dose intensification of CHOP are important advances in the treatment of NHL. The results of ongoing studies will refine further treatment options. The two more important questions for improving the outcomes in patients with DLBCL are how to recognize and treat patients with high risk of failure to R-CHOP or relapse after R-CHOP. Several ongoing studies are testing the above aspects and the results should be published in the next couple of years.

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