# First-line therapy of CD20+ diffuse large B-cell lymphoma: facts and open questions

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*doi:10.3324/haematol.2009.011320*

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, administered every 21 days (CHOP21), has been for years the standard therapy for advanced diffuse large B-cell lymphoma (DLBCL), with a long-term overall survival rate of about 40%.[1] Modifications of the CHOP design including its dose-intensity and dose-density, have been introduced in the attempt to improve its efficacy. The dose-intensive ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) regimen, developed by the *Groupe d'Etude des Lymphomes de l'Adult* (GELA) demonstrated an advantage over CHOP in terms of event-free and overall survival[2] and the CHOEP (CHOP plus etoposide) regimen developed by the German High-Grade non-Hodgkin's Lymphoma (DSHNHL) group proved to be superior to CHOP in young patients with normal lactate dehydrogenase (LDH).[3] Moreover, compared to CHOP21, the dose-dense two-weekly CHOP14 regimen produced longer survival in young and elderly patients.[4]

In the early 1990s, the prognostic relevance of a number of clinical variables was retrospectively evaluated by the International non-Hodgkin's Lymphoma Prognostic Factors Project in patients with diffuse lymphoma who had been given doxorubicin-containing regimens. An International Prognostic Index (IPI) was developed, based on the five most significant variables: age, clinical stage, LDH, ECOG performance status and number of extra-nodal sites.[5] Accordingly, four categories of risk were defined: low (0-1 risk factor), low-intermediate (2 factors), high-intermediate (3 factors) and high risk (4 or 5 factors). Each prognostic group showed significantly different outcomes, with 5-year relapse-free survival rates ranging from 70% to 40% and overall survival rates ranging from 73% to 26%. An adjustment of the original IPI system was subsequently developed for patients younger than 60 years (age-adjusted IPI or aaIPI); the risk factors considered were stage, LDH and performance status and risk categories varied from aaIPI 0 to aaIPI 2-3. The IPI system was of great help in designing clinical studies for different patient categories including young patients with favorable prognosis (aaIPI 0-1), young patients with intermediate/unfavorable prognosis (aaIPI 2-3) and elderly patients.

One of the facts that changed the therapeutic scenario in DLBCL was the coupling of CHOP chemotherapy with rituximab, a humanized anti-CD20 monoclonal antibody (R-CHOP). The role of rituximab was first evaluated in elderly (> 65 years) patients with DLBCL, in whom eight courses of R-CHOP every 21 days conclusively demonstrated, in a GELA study, to significantly improve the outcome compared with CHOP alone.[6] This superiority was evident in patients with both favorable and unfavorable IPI scores and the survival benefit is maintained over time. Of importance, the addition of rituximab did not substantially increase toxicity, although a trend towards a higher risk of infections after R-CHOP compared to CHOP was observed. The US E4494 Intergroup trial comparing up-front CHOP with or without rituximab and with or without rituximab maintenance in the elderly demonstrated a significant advantage for patients receiving rituximab, either as part of induction or maintenance therapy.[7] The impact of adding rituximab to CHOP, in both young and elderly patients with DLBCL, has been recently confirmed in a large population-based study. Comparing survival before and after the introduction of rituximab into clinical practice, the British Columbia Cancer Agency observed that in elderly patients the 2-year overall survival improved from 40% to 67% and progression-free survival from 44% to 67%, while in young patients overall survival improved from 69% to 87%, with a 10% gain in the progression-free survival.[8]

## What may be considered standard therapy for favorable IPI young patients?

The answer to this question has come from the results of the Mab-Thera International Trial (MInT) study.[9] This trial has definitely demonstrated that in young (<60 years) patients with low risk disease (aaIPI 0-1) six cycles of R-CHOP21 (or CHOP-like) are superior to CHOP21 (or CHOP-like) therapy, in terms of complete remission (86% *vs.* 68%), failure-free survival (83% *vs.* 53%) and overall survival (95% *vs.* 86%). Significantly different results were obtained according to aaIPI score: in patients with an aaIPI score of 0 and no bulky disease, the time to treatment failure and overall survival rates were 89% and 98%, respectively, whereas in patients with an aaIPI score of 1 and/or bulky disease, the corresponding rates were 76% and 91%, respectively. Subsequent trials are now dealing separately with the very favorable (aaIPI 0, without bulky disease) and favorable risk subgroups (aaIPI 1 and/or bulky disease). In the very low-risk category, the DSHNHL-FLYER trial is comparing six courses of R-CHOP21 with four courses of R-CHOP21 (with six doses of rituximab), while in the low-risk group, the DSHNHL-UNFOLDER trial is comparing six courses of R-CHOP14 with six courses of R-CHOP21. At the moment, six cycles of R-CHOP21 may be considered the standard therapy in low-risk young patients with DLBCL, as a whole; the mature results of the on-going studies will indicate the best therapy for prognostically different subgroups.

## What may be considered standard therapy for elderly patients?

The original experience with R-CHOP therapy was conducted by the GELA group in elderly patients. In

these patients, eight cycles of R-CHOP, administered every 21 days, proved superior to eight cycles of CHOP, with a good overall efficacy and a manageable toxicity.[6] The recently published results of the RECOVER-60 trial have added new information.[10] This trial compared, in a 2 x 2 factorial design, six versus eight cycles of CHOP14, with or without rituximab, in patients aged 61 to 80 (all patients received support with recombinant granulocyte colony-stimulating factor). The results indicate that six cycles of R-CHOP14 plus eight doses of rituximab significantly improved event-free, progression-free and overall survival compared to six cycles of CHOP14 and that eight cycles of therapy were not better than six. Based on this experience, six cycles of R-CHOP14, with granulocyte colony-stimulating factor support, may be viewed, at the moment, as the standard therapy for elderly patients in all IPI categories.

### Is R-CHOP14 the new standard?

A formal demonstration that R-CHOP14 is superior to R-CHOP-21 is lacking. A number of trials are comparing standard-dose R-CHOP21 with dose-dense R-CHOP14, including the UNFOLDER trial in young patients with favorable IPI (six cycles), the GELA LNH03-6B in elderly patients (eight cycles) and the UK-NCRI trial in all patient categories, with further stratification for IPI score (0-1 *vs.* 2-3 *vs.* 4-5) and age (< 60 *vs.* ≥60). Furthermore, R-CHOP21 is being compared with a dose-intensive regimen such as R-ACVBP14 in young patients with favorable IPI score (GELA LNH03-2B trial) and with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in the CALGB 50303 study, which includes a prospective gene profile analysis at diagnosis and restaging.

### Is there a role for up-front high-dose chemotherapy with autologous stem cell transplantation in unfavorable IPI young patients in the rituximab era?

No standard therapy has yet been established for patients younger than 60, with an intermediate/unfavorable aaIPI score of 2-3.

In the pre-rituximab era, no unequivocal superiority was demonstrated in randomized studies for up-front high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) over conventional or intensified chemotherapy in unfavorable DLBCL. A superiority for high-dose chemotherapy with ASCT was demonstrated in a retrospective analysis of patients with IPI score 2-3 by a GELA study,[11] and in patients with high-intermediate risk by a GOELAM study,[12] while other studies showed no survival benefit from high-dose chemotherapy over standard-dose therapy.[13,14] The discrepancies between the results of these randomized studies most likely derived from the different patient selection criteria (the IPI was applied retrospectively in most studies) and from the different intensity and duration of standard dose chemotherapy.

This scenario might have been modified by the introduction of rituximab. A number of non-randomized phase II studies demonstrated that a dose-dense approach incorporating rituximab without ASCT, namely R-CHOP14, is feasible with fairly good efficacy in young patients with intermediate-high aaIPI risk;[15,16] however, the reported progression-free survival rates do not exceed 60%, indicating the need for a more intensive approach such as intensified chemo-immunotherapy with rituximab-containing high-dose chemotherapy followed by ASCT. The paper by Vitolo *et al.*, published in this issue of the journal,[17] reports on the results of a phase II trial carried out by the *Gruppo Italiano Multiregionale Linfomi e Leucemie* to evaluate the combination of rituximab with dose-dense megaCEOP14 (epirubicin substituted for doxorubicin), followed by rituximab-coupled high-dose chemotherapy (MAD: mitoxantrone, high-dose cytarabine and dexamethasone) and BEAM with ASCT in untreated young patients with intermediate/high aaIPI score. The results demonstrate that rituximab-containing high-dose chemotherapy and ASCT was feasible and effective as up-front therapy in a large cohort of patients, producing a complete response rate of 82% and 4-year freedom from progression and overall survival rates of 73% and 80%, respectively. The patient drop-out rate from this study for toxicity or progression was 19% which is similar to the 20% reported after dose-dense R-CHOP14.[15] The results of this protocol were also compared with those of a historical control group of patients with the same prognosis treated up-front with high-dose chemotherapy and ASCT, without rituximab. With the limitations of historical control, the regimen including rituximab proved to be significantly superior to that without rituximab. This study has set the stage for the on-going phase III randomized study by the *Intergruppo Italiano Linfomi* (DLCL-04) comparing in a 2 x 2 factorial design, full-course rituximab-coupled dose-dense chemotherapy (eight cycles of R-CHOP14, or six cycles of R-megaCHOP14) with shortened (four courses) rituximab-coupled dose-dense chemotherapy followed by rituximab-additioned high-dose chemotherapy and ASCT.

A number of trials are under way in young patients with unfavorable IPI score. Apart from the LNH03-3B GELA study which is a non-randomized trial adopting four cycles of dose-intensive R-ACVBP + high-dose methotrexate and ASCT, most studies do randomize dose-dense immuno-chemotherapy versus up-front rituximab-high-dose chemotherapy with ASCT. A *Gruppo Italiano Terapie Innovative dei Linfomi* (GITIL) trial is comparing eight cycles of R-CHOP14 with a rituximab-supplemented high-dose sequential chemotherapy regimen. The German High-Grade non-Hodgkin Lymphoma Study Group is comparing eight cycles of dose-dense R-CHOEP14 with progressively dose-escalated R-CHOEP followed by repeated stem cell transplants to achieve maximal dose intensity and an *in vivo* purging effect. Other phase III randomized studies evaluating up-front rituximab+high-dose chemotherapy with ASCT include the US Intergroup S9704 trial comparing eight cycles of R-CHOP21 *vs.* five cycles of R-CHOP21 + ASCT and a GOELAM trial comparing eight cycles of R-CHOP14 *vs.* two cycles of R-CEEP (cyclophosphamide, epirubicin, vindesine, prednisone) + high-dose methotrexate/cytarabine + ASCT.

### Does rituximab modify the predictive value of prognostic factors?

The redistribution of the original IPI factors in patients treated with R-CHOP into a revised score (R-IPI) distinguishes three prognostic categories, with different 4-year survival rates ranging from 94% for very good risk patients (no risk factors) to 79% for good risk patients (1-2 risk factors) and 55% for poor risk patients (3-5 risk factors).[18] The R-IPI does not, however, discriminate patients with less than 50% probability of survival and this limits its clinical utility.

The addition of rituximab to CHOP has modified the prognostic significance of bcl-2 protein expression; in the pre-rituximab era, the expression of bcl-2 protein was associated with a poor prognosis, while R-CHOP is able to overcome the bcl-2-associated chemo-resistance.[19] The introduction of rituximab has also weakened the significance of other prognostic indicators such as bcl-6, p53 and of the immunohistochemical phenotype. These examples indicate how, with new therapies, the single prognostic factors should be re-interpreted and new predictors should be introduced into clinical practice.

### Does interim positron emission tomography have a predictive value?

Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET) has widely been introduced as a mean of functional imaging in lymphoma. However, at variance with Hodgkin's lymphoma, unequivocal data are not available on the predictive capacity of this procedure in DLBCL. In a GELA study, PET-negative patients after two cycles of anthracycline-based therapy had significantly better event-free survival (82% *vs.* 43%) and overall survival (90% *vs.* 61%) compared to patients remaining positive at the interim PET analysis.[20] Accordingly, an early PET-oriented approach is being adopted in the on-going LNH 07-3B GELA trial comparing R-CHOP14 to R-ACVBP14 in young patients with aaIPI 2-3. In this trial, two interim PET scans are carried-out after two and four cycles of therapy; patients remaining PET-positive after the fourth course are shifted to early salvage with the CORAL protocol. The most crucial problem with interim PET analysis in DLBC is its low positive predictive value. Indeed, in a MSKCC phase II trial of dose-dense R-CHOP14 followed by risk-adapted consolidation (ICE or ICE+ASCT), 36% of patients were positive at the interim PET analysis (after four cycles of R-CHOP14), of which only 13% had a positive biopsy for residual disease; the positive predictive value of interim PET in this experience was, therefore, lower than 20%.[21] In another series,[22] positive interim PET after two cycles of R-CHOP was not predictive, whereas end of therapy PET strongly correlated with progression-free survival. This implies that interpretation criteria for interim PET need to be standardized and that, at the moment, only the negative predictive value of interim PET seems to be clinically applicable.

### What is the optimal use of rituximab?

Although the introduction of rituximab represents a major breakthrough in the therapy of B-cell lymphomas, we do not yet know its optimal schedule. Rituximab serum levels build up rather slowly; it is, therefore, plausible that a dose-dense administration of this antibody could improve its efficacy. Such intensified use of rituximab is being explored both in the US (ECOG study) and Germany. A dose-intense rituximab version of R-CHOP14 (DENSE-R-CHOP14) has been devised by the German group and includes four doses of rituximab during the first cycle of CHOP14, three doses during the second cycle and one dose per cycle, thereafter. Six cycles of DENSE-R-CHOP14 (with conventional or liposomial vincristine) are now being compared to six cycles of R-CHOP14 (with conventional or liposomial vincristine) in elderly patients (> 60 years) in a new 2 x 2 factorial RECOVER-60 trial. Furthermore, because RECOVER-60 results[10] indicated that male gender adversely affects progression-free survival in the rituximab treatment arms, the rituximab dose of 375 mg/m$^2$ per administration is being up-graded in males to 500 mg/m$^2$ in a DENSE-R-UP-CHOP14 regimen.

A warning must be raised about an increased risk of infections after dose-dense rituximab. Although an increased incidence of infections was not observed during the three-weekly R-CHOP21, the situation is different after bi-weekly R-CHOP14 and, in particular, after dose-intense rituximab or rituximab-supplemented high-dose chemotherapy. Indeed, an increased risk of interstitial pneumonia was recorded after R-CHOP14[15] and appropriate antibacterial and anti-*Pneumocystis* prophylaxis is mandatory.

### Does immuno-chemotherapy reduce the risk of central nervous system disease?

The analysis of central nervous system (CNS) events occurring in elderly patients treated in the RECOVER-60 trial indicated that the addition of rituximab to CHOP reduced the risk of CNS disease.[23] The guidelines of the Italian Society of Hematology for management of nodal DLBCL have stated that patients with unfavorable IPI score and involvement of bone marrow and/or more than one extranodal site of disease are at high risk of CNS disease and should be given CNS prophylaxis with intrathecal methotrexate;[24] in the RECOVER-60 trial, however, intrathecal methotrexate failed to further reduce the risk of CNS disease in patients treated with R-CHOP14, with the possible exception of patients with testicular lymphoma. Because a comparison of the different forms of CNS prophylaxis has never formally been conducted, the question of the optimal prophylactic procedure is still open.

### Perspectives with new drugs

One of the most promising new approaches in the therapy of CD20+ DLBCL is represented by the use of radio-immunotherapy. The radio-immunoconjugate $^{90}$Y-ibritumomab-tiuxetan (Zevalin®) was shown to be active in elderly patients with relapsed or refractory DLBCL, with an overall response rate of 52% in patients pretreated with rituximab and not eligible for ASCT.[25] Data from phase II trials in elderly patients indi-

cate that Zevalin is effective as consolidation after CHOP[26] or R-CHOP[27] and a phase III randomised trial (ZEAL study) is evaluating the efficacy and safety of subsequent Zevalin versus observation in elderly patients with DLBCL in remission after R-CHOP. Moreover, $^{90}$Y-ibritumomab-tiuxetan has been utilized to improve the efficacy of the BEAM preparative regimen prior to ASCT,[28] and high-dose $^{90}$Y-ibritumomab-tiuxetan with tandem stem cell reinfusion proved to be a tolerable and applicable myeloablative regimen for ASCT.[29]

Different new drug categories are being investigated in phase I-II studies and include the anti-angiogenic agents bevacizumab and lenalidomide and the proteasome inhibitor bortezomib. R-CHOP with added bevacizumab is being compared to R-CHOP alone, while lenalidomide maintenance will be compared to placebo in patients responding to first-line R-CHOP.

## Conclusion

The vast heterogeneity of DLBCL is a continuous challenge for basic researchers and clinicians. New correlations between biological features, response to therapy and outcome are being investigated and may serve as a background for new prospective trials. Mature data on first-line therapy are available for low-risk young patients and elderly patients; for young patients with unfavorable prognosis, the results of the on-going clinical trials are awaited to draw reliable conclusions.

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## Immune dysfunction in chronic lymphocytic leukemia T cells and lenalidomide as an immunomodulatory drug

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Developing more effective therapeutic options and treatment regimes for patients with chronic lymphocytic leukemia (CLL) is the subject of on going international clinical studies involving chemo-immunotherapy approaches that incorporate monoclonal antibodies such as rituximab (anti-CD20). Results have demonstrated remarkably improved clinical response rates for CLL patients receiving such treatment regimes.[1] To aid the pursuit of curative treatment strategies, particularly for relapsed patients who are unlikely to respond to standard approaches, novel agents for CLL are required. Immune therapy represents a promising treatment approach,[2] as demonstrated by the improved results in CLL with chemo-immunotherapy and successful demonstration of a graft-versus-leukemia effect after allogeneic stem cell transplantation leading to long-term clinical remissions.[3] However, CLL is associated with immune dysfunction and it is becoming increasingly clear that CLL tumor cells co-opt immunosuppressive mechanisms to evade immune recognition. For example, although CLL cells express tumor antigens that can be presented by major histocompatibility complex (MHC) class I and class II molecules, an effective immune response is not elicited against the tumor cells.[4,5] This likely contributes to the clinical pattern of a progressively growing tumor population over time. The failure to mount an effective immune response can be explained, in part, by a lack of effective antigen presentation, as manifested by low levels of expression of adhesion and co-stimulatory molecules essential for the induction of effective immune responses. In addition, CLL cells are known to secrete immunosuppressive cytokines such as interleukin (IL)-6 and IL-10. Thus, repairing the immune dysfunction in CLL is an essential step in order to harness and promote immune cell-mediated anti-cancer responses.

A new agent that is being used in CLL and is receiving considerable interest is the second- generation immunomodulatory drug, lenalidomide (Revlimid; Celgene). Lenalidomide is designed to enhance the immunological and anti-cancer properties of its parent drug thalidomide, while attenuating neurotoxic adverse reactions. Lenalidomide has been shown to be clinically effective as a single agent in relapsed and refractory CLL patients,[6,7] and ongoing clinical trials are also assessing its efficacy in previously untreated patients. The precise anti-CLL mechanism of action of lenalidomide is not yet completely defined. Potential mechanisms of action include blockade of angiogenesis and pro-tumor cytokines, inhibition of stromal cell-CLL cell interactions, and enhancement of immune cell function including that of T cells, monocytes and NK cells. Of note, in contrast to lenalidomide's anti-tumor activity in multiple myeloma, no direct *in vitro* pro-apoptotic effect of lenalidomide has been observed using primary CLL cells.[8]

Uniquely in CLL, the use of lenalidomide is associated with a tumor flare reaction that has been postulated to be associated with a drug-induced, immune-mediated anti-tumor response. This tumor flare reaction is manifested as an acute onset of swelling of involved