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## Front-line Therapy for Nonlocalized Diffuse Large B-cell Lymphoma: What Has Been Demonstrated and What Is Yet to Be Established

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### Abstract

The field of treatment of diffuse large B-cell lymphoma has been in a continuous flux over the last 10-15 years owing to the introduction of new therapeutic approaches such as dose-dense chemotherapy, monoclonal antibodies and high-dose chemotherapy followed by autologous peripheral blood stem cell transplant. The use of clinical prognostic factors has improved our ability to predict the outcome of these lymphomas; moreover, the gene and protein expression pattern has been shown, at least in the pre-rituximab era, to be an independent and powerful prognostic indicator. This review will focus on results obtained in the last decade by large clinical trials evaluating the first-line therapy in nonlocalized diffuse large B-cell lymphoma; special emphasis will be placed on more mature results that can be indicated as 'standard' therapy. Ongoing studies addressing as yet unanswered or controversial questions will be analyzed, and preliminary data will be critically reviewed.

### Definition & Heterogeneity of Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a neoplasm of the germinal center B lymphocytes with a diffuse growth pattern and a high-intermediate proliferation index. DLBCLs represent approximately 30% of all lymphomas and, according to the WHO classification,<sup>[1]</sup> may present with several morphological variants including the centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic and plasmoblastic subtypes. Clinically, along with the not otherwise specified forms, DLBCL encompasses subtypes such as the primary mediastinal lymphoma of thymic origin and the intravascular B-cell lymphoma. In all variants, immunophenotyping invariably shows the presence of B-cell markers, such as CD20, CD19 and CD22 antigens, while the gene and protein expression pattern is rather variable. The bcl-2 protein is expressed in approximately 50% of cases and the bcl-6 protein in approximately 70% of all patients, consistently with a germinal center origin.<sup>[2]</sup> Median age at diagnosis in the different cohorts ranges from 60 to 65 years; approximately two-thirds of patients present with advanced stage disease, 40% in extranodal sites; bone marrow is involved at diagnosis in 15% of cases.<sup>[1,3]</sup>

### Clinical Prognostic Factors

Anatomical staging is not a sufficient predictor of the outcome of aggressive non-Hodgkin's lymphoma. 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<sup>[4]</sup> in a large series of patients with aggressive lymphoma. Patients belonged to the histological category that we now define as DLBCL and all had been given doxorubicin-containing regimens. A prognostic system was designed considering the presence or the absence at diagnosis of the five most significant variables in a univariate analysis and calculating a prognostic score for each individual patient (International Prognostic Index [IPI]). The risk factors considered in this model were age over 60 years,

advanced clinical stage (III-IV), serum lactate dehydrogenase (LDH) level above normal, Eastern Cooperative Oncology Group (ECOG) performance status over 1 and presence of more than one extranodal site of disease. Accordingly, four prognostic categories were defined: low (zero or one factor), low-intermediate (two factors), high-intermediate (three factors) and high risk (four or five factors). Each prognostic group showed a different rate of complete response and a significantly different outcome, with 5-year relapse-free survival ranging from 70 to 40% and overall survival (OS) ranging from 73 to 26%. An adjustment of the original IPI system was subsequently developed for patients younger than 60 years (age-adjusted IPI [aalPI]); the risk factors considered in the aalPI are advanced stage, higher than normal LDH serum level and performance status over 1. The aalPI identifies four distinct groups (0-3) according to the number of risk factors. [Table 1](#) shows that different groups have different outcomes when treated with doxorubicin-containing chemotherapy (CT).

## Clinical Applicability & Utility of Biological Prognostic Factors

Although the IPI system represents substantial progress in defining the prognosis of DLBCL compared with the classical anatomical stage, clinical prognostic factors are only surrogate indicators of the variability of the underlying lymphoma at the biological level. A long list of putative biological prognostic markers can be compiled, including apoptotic proteins (bcl-2 and caspases), cell-cycle regulatory molecules (cyclin-D, Ki-67 and p53) and B-cell differentiation markers such as bcl-6, adhesion and angiogenetic molecules.<sup>[5]</sup> However, the clinical applicability and utility of most of these markers is far from being univocally determined, with the only possible exceptions of bcl-2 and bcl-6. The retrospective nature of most studies on biological predictors and the involvement of multiple biologic processes and regulatory mechanisms limits the clinical relevance and predictability of each single molecule.

The heterogeneity of DLBCL has recently been highlighted by gene-expression profiling studies using DNA micro-arrays to distinguish lymphoma subtypes based on mRNA expression profiles.<sup>[6,7]</sup> With this technology, at least two distinct subtypes have been differentiated, the germinal center B-cell-like (GBC) and the activated B-cell-like (ABC) DLBCL. When treated with cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) or CHOP-like regimens, patients with the GBC profile have a significantly better 5-year OS compared with those with the ABC profile (60 vs 35%;  $p < 0.001$ ), and this is independent of the IPI score.<sup>[7]</sup> A distinct molecular signature characterizes the primary mediastinal B-cell lymphoma, which differs from other DLBCLs and shares features with classical Hodgkin's lymphoma.<sup>[8]</sup> Several models based on gene-expression data have been developed in the pre-rituximab era using a limited set of 'predictive' genes (down to six), independently of the IPI index.<sup>[9,10]</sup> More recently, the focus has shifted from RNA to protein expression (proteomics) and a confirmation of the molecular classification of DLBCL has been provided by the study of the expression of three proteins (CD10, bcl-6 and MUM-1) using immunochemistry in a tissue-microarray analysis.<sup>[11]</sup>

As all data on the outcome predictability of the gene-expression profile in DLBCL have been accumulated in the pre-rituximab era, prospective studies should re-evaluate the prognostic significance of molecular subclassification after the introduction of rituximab. If confirmed on a large scale, the predictive capacity of the molecular profile should pave the way for a tailored therapy according to both clinical and molecular markers.

## CHOP Chemotherapy & Beyond

The CHOP combination CT, administered every 21 days, has been the standard regimen for the treatment of advanced DLBCL for many years,<sup>[12,13]</sup> producing long-term disease-free survival in approximately 35% of patients. New regimens were developed in an attempt to improve on original CHOP results; these regimes incorporated up to eight non-cross-resistant drugs and antimetabolites at high doses. Monoinstitutional successes were initially reported,<sup>[14,15]</sup> until a large US intergroup randomized study failed to conclusively demonstrate superiority for any of the new generation regimens (MACOP-B, ProMACE-CytaBOM and m-BACOP) over CHOP.<sup>[16]</sup> After this trial, the CHOP regimen was assumed as the standard therapy for DLBCL.

Modifications of the original CHOP design were further introduced to possibly improve on its results, and concerned both dose intensity and dose density (the interval between courses).<sup>[17,18]</sup> In poor-prognosis aggressive non-Hodgkin lymphoma, the Group d'Etude des Lymphomes de l'Adult (GELA) has developed the dose-intensive doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) regimen, with an advantage over CHOP in terms of both event-free and overall survival.<sup>[19]</sup> However, this benefit was in part counterbalanced by an increased acute toxicity and treatment-related mortality and by a higher risk of developing late myelodysplasia and acute leukemia.<sup>[20]</sup>

The German High-Grade non-Hodgkin Lymphoma Study Group (DSHNHL) has added etoposide to CHOP (CHOEP regimen) and compared 2-weekly CHOP14, with or without etoposide, versus 3-weekly CHOP21, with or without etoposide, in two large four-arm randomized studies in young (<60 years) patients with normal LDH and in elderly patients with aggressive lymphoma.<sup>[21,22]</sup> Evidence has been provided that CHOEP (either every 2 or 3 weeks) is superior to CHOP in young patients with normal LDH, and that dose-dense CHOP14 produces a longer survival compared with CHOP21, both in young and elderly patients. The need for granulocyte-colony stimulating factor (G-CSF) support to allow the CHOP14 regimen to be administered on time at the planned dose had been underlined in a prior Southwest Oncology Group Phase II study.<sup>[23]</sup> In the DSHNHL studies, patients treated with the 2-weekly regimens (either CHOP or CHOEP) received filgrastim from days 4 to 13. With G-CSF support, the hematological toxicity of CHOP14 and CHOP21 was comparable and, owing to its efficacy and toxicity profile, CHOP14 was considered the standard therapy for patients older than 60 years.

The Dutch-Belgian Hemato-Oncology Cooperative (HOVON) group has compared the standard CHOP with an intensified CHOP14 in patients with intermediate risk and found a survival advantage for intensified CHOP only in the subgroup of low-intermediate risk patients, whereas patients belonging to the high-intermediate group did not have additional benefit from the intensified CHOP. The provisional conclusion of this study was that, for younger patients with unfavorable IPI aggressive lymphoma, the optimal dose and timing of CT remains to be determined.<sup>[24]</sup>

## High-dose Chemotherapy With Autologous Stem Cell Rescue as Part of Front-line Therapy

A different attempt at improving on CHOP results consisted of the introduction of high-dose CT followed by autologous stem cell transplantation as part of up-front therapy in young patients with unfavorable IPI, or in patients achieving a partial response with CHOP. A number of randomized trials have been conducted to compare standard-dose versus standard plus high-dose CT and autologous stem cell transplantation (ASCT) in these patient categories. Unfortunately, no univocal and conclusive results have yet been achieved, as recently underlined by a large meta-analysis.<sup>[25]</sup> A number of studies showed no survival benefit for high-dose CT over standard-dose therapy,<sup>[26-31]</sup> whereas other trials showed a survival (event-free and overall) advantage for high-dose CT<sup>[32-34]</sup> and one single trial showed an advantage for standard-dose CT.<sup>[35]</sup> Of interest, the GELA study<sup>[33]</sup> only demonstrated a superiority for high-dose CT with ASCT in a retrospective subgroup analysis of patients with an IPI score of 3 or more, and the GOELAM study<sup>[34]</sup> only in patients with high-intermediate risk according to IPI. The discrepancies between all randomized studies derive mostly from the different patient selection criteria (the IPI in most studies was applied only retrospectively) and from the different intensity and duration of 'standard' CT. Moreover, high-dose CT with ASCT was not equally timed in the different trials: some utilized ASCT as consolidation of a previously achieved complete response, others as intensification of a shortened induction therapy, or as induction of remission in patients who had a slow or a partial response to standard-dose CT. These different approaches significantly biased the comparative analysis reliability and held back definitive conclusions.<sup>[36]</sup>

## Role of Immunochemotherapy

One of the facts that changed the therapeutic scenario in DLBCL was the introduction of rituximab, a humanized anti-CD20 monoclonal antibody. The role of rituximab was first evaluated in elderly (>65 years) patients with DLBCL; in this category of patients, the addition of rituximab to conventional CHOP (administered every 21 days, at standard doses), has been conclusively demonstrated, in a multi-institutional GELA study, to lead to a significant improvement in outcome.<sup>[37]</sup> In this study, eight cycles of rituximab-CHOP (R-CHOP) produced a complete response in 75% of patients versus 63% of CHOP alone ( $p = 0.005$ ), with a significant 5-year survival benefit in terms of event-free (47 vs 29%), progression-free (54 vs 30%) and overall survival (58 vs 45%). The superiority of R-CHOP over CHOP alone was evident both in patients with favorable and unfavorable IPI scores, and this survival benefit was maintained over time, as was recently confirmed by the 5-year update of the GELA data.<sup>[38]</sup> Moreover, the addition of rituximab did not substantially increase the toxicity of CHOP, even though a trend towards an increased risk of infections was observed after R-CHOP compared with CHOP. A cooperative American study in elderly patients comparing up-front CHOP with or without rituximab and with or without rituximab maintenance confirmed the GELA results, with a significant advantage for patients receiving rituximab, either as part of induction or maintenance therapy.<sup>[39]</sup>

After demonstrating that CHOP14 is superior to CHOP21 in elderly patients, the German cooperative group has compared six versus eight cycles of CHOP14, with or without rituximab in patients with DLBCL, aged 61-80 years (RICOVER-60 study, with a 2 × 2 factorial design). Six cycles of R-CHOP14 significantly improved the event-free,

progression-free and overall survival over six cycles of CHOP-14. Of the four regimens assessed in this study, six cycles of R-CHOP-14 proved to be the best treatment for elderly patients, with which other approaches should be compared.<sup>[40]</sup>

A role for rituximab coupled with CHOP or CHOP-like regimens has been demonstrated in patients younger than 60, with a favorable IPI score by the Mab-Thera International Trial (MInT) study.<sup>[41]</sup> The MInT trial has compared six cycles of standard CHOP or CHOP-like therapy with six cycles of the same CT added with rituximab and demonstrated an advantage for the antibody group in terms of complete response rate (86 vs 68%), failure-free (83 vs 53%) and overall survival (95 vs 86%). Significantly different results have been obtained according to the IPI score: in patients with IPI 0 and no bulk, time to treatment failure (TTF) and OS were 89 and 98%, respectively, whereas in patients with IPI 1 and/or bulky disease, TTF and OS were 76 and 91%, respectively.

The impact of adding rituximab to CHOP, in both young and elderly patients with DLBCL, has recently been confirmed in a large population-based study. Comparing survival before and after the introduction of rituximab into the clinical practice, the British Columbia Cancer Agency observed that, in elderly patients, the 2-year OS improved from 40 to 67% and progression-free survival from 44 to 67%, while, in young patients, the OS improved from 69 to 87%, with a 10% gain in the progression-free survival.<sup>[42]</sup>

All these studies have contributed substantially to establishing the new standard of therapy in different categories of patients with DLBCL. [Table 2](#) concisely summarizes the provisional state-of-the-art according to patient categories and IPI scores.

No standard therapy has yet been established for patients aged under 60 years with unfavorable IPI score. In this category of patients, a number of Phase II studies have demonstrated that a dose-dense approach, incorporating rituximab, with G-CSF support (either with filgrastim, lenograstim, or peg-filgrastim) is feasible, with optimal dose intensity and good efficacy.<sup>[43-46]</sup>

## **Does Rituximab Modify the Predictive Value of Prognostic Factors?**

The IPI prognostic model does retain its predictive capacity in patients treated with R-CHOP (R-IPI). The redistribution of the original IPI factors into a revised IPI distinguishes three prognostic categories, with different 4-year survivals, ranging from 94% for very good risk (no risk factors) to 79% for good risk (one to two risk factors) and 55% for poor risk (three to five risk factors) subgroups. However, the R-IPI does not discriminate patients with less than 50% probability of survival and needs to be assisted by new biological and clinical prognostic factors, validated in prospective clinical trials.<sup>[47]</sup>

Several groups have reported that bcl-6 protein expression alone or in combination with other germinal center markers predicts for a favorable outcome in patients with DLBCL treated with CHOP CT. In a US intergroup trial,<sup>[48]</sup> the addition of rituximab to CHOP has modified the prognostic significance of bcl-6 protein expression: bcl-6-negative patients showed improved outcome with R-CHOP compared with CHOP alone, whereas bcl-6-positive patients had a favorable outcome even when treated with conventional CHOP alone.

The expression of the bcl-2 protein has been associated with poor prognosis in patients with DLBCL.<sup>[49]</sup> The significance of bcl-2 over-expression has been re-evaluated in patients treated with R-CHOP in a GELA study.<sup>[50]</sup> R-CHOP was associated with a significantly better event-free survival compared with CHOP alone in bcl-2-positive but not in bcl-2-negative patients. These results suggest that rituximab plus CHOP is able to overcome bcl-2-associated resistance to CT in patients with DLBCL with bcl-2 protein overexpression. These examples indicate how, with new therapies, single prognostic factors should be re-interpreted and new predictors should be introduced into the clinical practice.

## **Fluorine-18-fluoro-deoxy-glucose-PET Scan as a Prognostic Indicator**

Fluorine-18-fluoro-deoxy-glucose (FDG) PET has been widely introduced as a means of functional imaging in aggressive lymphoma. A number of studies have demonstrated that early restaging with FDG-PET after one to four

cycles of doxorubicin-based CT is predictive of outcome.<sup>[51-53]</sup> In particular, in a GELA study,<sup>[53]</sup> PET-negative patients after two cycles of anthracycline-based therapy had significantly better event-free survival (EFS; 82 vs 43%) and OS (90 vs 61%) compared with patients remaining PET-positive. FDG-PET scan proved to be more predictive than IPI score and is now being evaluated in the different phenotypic subtypes of DLBCL. Even though further studies are needed to define its optimal timing during therapy and to standardize interpretation criteria (mostly concerning the problem of false positivity), the FDG-PET scan has become an essential tool for response evaluation and prognostic assessment in DLBCL.<sup>[54,55]</sup>

## Ongoing Phase III Studies

Several Phase III randomized studies are on-going in DLBCL; the most important of them are listed in [Table 3](#). Most are tailored according to the different IPI categories, only a minority include all DLBCL patients, with subsequent stratification according to age and IPI. In most studies, a pretherapy evaluation of protein expression with tissue microarray analysis is performed to correlate the proteomic profile with outcome. Besides, baseline and early (usually after two cycles of therapy) FDG-PET scans are planned.

As far as young patients (<60 years) are concerned, the MInT successor trials do separate a very favorable (IPI 0, no bulk) from a favorable subgroup (IPI 1 or bulk). The DSHNHL-FLYER study deals with the very favorable category and compares six cycles of R-CHOP21 with four cycles of R-CHOP21 (with six doses of rituximab), while the DSHNHL-UNFOLDER study compares in the favorable category six cycles of R-CHOP14 with six cycles of R-CHOP21. A rather similar approach is being followed by the GELA group comparing eight cycles of R-CHOP21 versus eight cycles of R-ACVBP cycles in young patients with aIPI 1. A number of trials are comparing standard-dose R-CHOP21 with dose-dense R-CHOP14 (UNFOLDER study in young patients; GELA and HOVON studies in elderly patients), or with other dose-intensive regimens such as ACVBP in a GELA study or DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in a Cancer and Leukemia Group B (CALGB) study, where patients are characterized with tissue microarray technology at diagnosis and restaging. Other studies randomize treatments of different duration (four vs six cycles or six vs eight cycles of standard or dose-dense R-CHOP) such as the FLYER study or the UK National Cancer Research Institute trial that compares eight cycles of R-CHOP21 versus six cycles of R-CHOP14 (with eight doses of rituximab); in this latter study, all risk categories are eligible, with further stratification for IPI score (0-1 vs 2-3 vs 4-5) and for age (<60 vs ≥60 years). In elderly patients (>65 years), the GELA group is comparing eight cycles of R-CHOP14 to eight cycles of R-CHOP21, while the HOVON group is comparing eight to six cycles of R-CHOP-14.

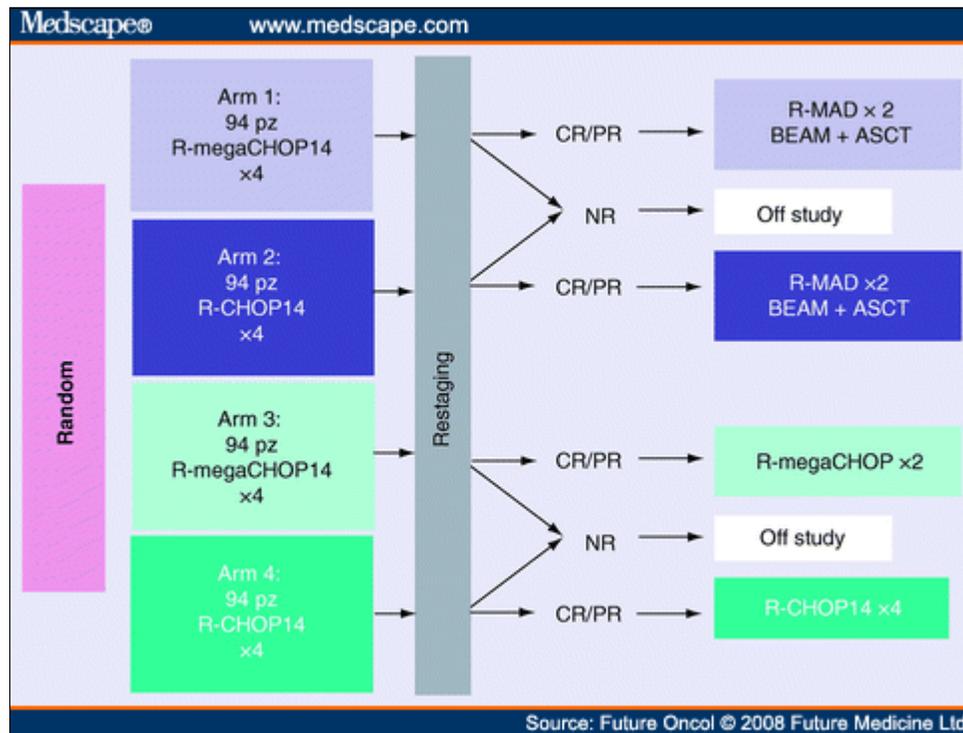
Most of the ongoing studies concern the category of patients aged less than 60 years, with unfavorable IPI score (aIPI 2-3), for whom no standard therapy has yet been established by clinical trials. In most of these studies, a dose-dense immunochemotherapy is compared with immunochemotherapy followed by up-front high-dose CT followed by ASCT (see the next section).

## Is There a Role for Up-front Autologous Stem Cell Transplantation in Young Patients With Unfavorable International Prognostic Index in the Rituximab Era?

In pre-rituximab era, no univocal superiority has been demonstrated for high-dose CT followed by ASCT over conventional or intensified CT in patients aged under 60, with unfavorable IPI. This scenario might have been modified by the introduction of immunochemotherapy, with the addition of rituximab to CT.

The results of a German Phase II study on dose-escalated CHOEP (mega CHOEP) followed by repeated stem cell transplantation as up-front treatment of unfavorable (elevated serum LDH) aggressive lymphoma (most of them were DLBCL) have recently been published.<sup>[56]</sup> The notions supporting this study were those of a maximal dose-density through a progressive dose escalation (cyclophosphamide up to 6 g/m<sup>2</sup> and etoposide up to 1480 mg/m<sup>2</sup>), of a very early intensification, and of a repeated collection and transplantation of autologous stem cells to exploit the *in vivo* purging effect of high-dose CT. The results obtained demonstrate the feasibility and the efficacy of this approach; therapy was stopped in 14% of patients for toxicity, and treatment-related mortality was 4%. The 5-year OS was 67% and freedom from treatment failure was 62%. A randomized Phase III trial of the German group is now comparing dose-dense eight cycles of R-CHOEP14 with dose-escalated R-CHOEP with repeated stem cell transplantation.

The outline of a Phase III randomized study of the Intergruppo Italiano Linfomi is illustrated in Figure 1. The background for this study consists on the demonstration that R-dose-dense CHOP14 with G-CSF support is feasible and effective in DLBCL,<sup>[45]</sup> and that rituximab as adjuvant to dose-dense and high-dose CT followed by up-front autologous transplantation improves the outcome of poor-prognosis DLBCL patients.<sup>[57]</sup> This four-arm study, with a 2 × 2 factorial design, compares R-dose-dense CT (eight cycles of R-CHOP14 or six cycles of intensified R-megaCHOP14, cyclophosphamide 1200 mg/m<sup>2</sup>, doxorubicin 75 mg/m<sup>2</sup>) with the same R-CT (four cycles of R-CHOP14 or R-megaCHOP14) followed by dose-intensification with two cycles of R-MAD (mitoxantrone 8 mg/m<sup>2</sup>/day × 3 days, cytarabine 2000 mg/m<sup>2</sup> every 12 h × 3 days and dexamethasone 4 mg/m<sup>2</sup>/day × 3 days), BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan) as a conditioning regimen and ASCT. In a prior Phase II study, the experimental transplant arm has proved to have a manageable toxicity and the MAD regimen an optimal mobilizing capacity.<sup>[58]</sup> Candidates are patients aged under 60 years, with aaIPI 2-3 DLBCL or grade 3B follicular lymphoma; the primary end point is 2-year failure-free survival.



**Figure 1.**

Outline of the Intergruppo Italiano Linfomi (IIL) Phase III randomized study on aaIPI of two to three young patients with diffuse large B-cell lymphoma. ASCT = Autologous stem cell transplantation; BEAM = Carmustine, etoposide, cytosine arabinoside and melphalan; CHOP = Cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; CR = Complete response; MAD = Mitoxantrone, cytarabine and dexamethasone; NR = No response; PR = Partial response; R = Rituximab.

The Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) is comparing R-CHOP14 × 8 cycles as the standard arm with an experimental arm consisting of a rituximab-supplemented high-dose sequential CT (R-HDS). A prior Phase II study demonstrated a prolonged survival in poor-risk (aaIPI 2-3) DLBCL with front-line R-HDS, an early-intensified CT with multiple autologous hematopoietic stem cell support.<sup>[59]</sup> Other Phase III randomized studies include the US Intergroup study that compares eight cycles of R-CHOP21 versus five cycles of R-CHOP21 plus ASCT and the Groupe Ouest Est Leucémies Aiguës Myéloblastiques (GEOLAM) study comparing eight cycles of R-CHOP14 versus two cycles of R-CEEP (cyclophosphamide, epirubicin, vindesine, prednisone) plus HDMTX/Ara-C + ASCT (see Table 3).

## Optimal Use of Rituximab

Although the introduction of rituximab has represented a major breakthrough in the therapy of B-cell lymphoma, we do not yet know which is 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 is being explored both in the USA (ECOG study) and in Germany. In particular, the German study compares, in elderly patients (>60 years), six cycles of R-CHOP14 with six cycles of CHOP14 supplemented with dose-intense rituximab consisting of four doses of the antibody during the first cycle of CHOP14, three doses during the second cycle and one dose per cycle thereafter. A warning should be raised towards the increased risk of infections in this setting. Although an increased incidence of infectious complications has not substantially been demonstrated after the 3-weekly R-CHOP21, the situation may be different during the bi-weekly R-CHOP14 or during rituximab-supplemented high-dose CT. In both circumstances,<sup>[45,59]</sup> a higher susceptibility to infections, with an increased risk of interstitial pneumonia has been recorded and the need for appropriate prophylaxis emphasized.

## CNS Prophylaxis

Systemic immunochemotherapy does not limit the risk of CNS involvement in aggressive lymphoma.<sup>[60]</sup> Patients with unfavorable IPI score and involvement of more than one extranodal site are at a much higher risk of CNS disease, and should therefore be given CNS prophylaxis with intrathecal methotrexate injections.<sup>[36]</sup> Specific extranodal sites appear to be more frequently associated with CNS involvement and include testes, paranasal sinuses, hard palate, orbit, paravertebral masses and bone marrow.

## Conclusion

The vast heterogeneity of DLBCL is a continuous challenge for both basic researchers and clinicians. New correlations between biological features, response to therapy and outcome are being investigated and represent the background for new prospective trials. Mature data from randomized clinical trials are available for some prognostic categories of patients (young with favorable prognostic index or elderly patients); for young patients with unfavorable prognostic index, clinical data are still preliminary and a longer follow-up is needed to draw reliable conclusions.

## Future Perspective

The future of therapy for DLBCL may consist of both the introduction of new drugs and molecules to optimize the results of standard CT and on improving the applicability and the role of up-front high-dose CT followed by ASCT. One of the most promising new approaches is represented by the use of radio-immunotherapy. The radio-immunoconjugate <sup>90</sup>Y-ibritumomab-tiuxetan (Zevalin<sup>®</sup>) was shown to be active in relapsed or refractory elderly patients with DLBCL, with an overall response rate of 52% in patients pretreated with rituximab and deemed not eligible for ASCT.<sup>[61]</sup> These results support a further evaluation of <sup>90</sup>Y-ibritumomab-tiuxetan activity as early consolidation in elderly DLBCL. In a recent Phase II trial, untreated elderly patients with DLBCL received six courses of CHOP and were further consolidated with <sup>90</sup>Y-ibritumomab-tiuxetan.<sup>[62]</sup> An ongoing Phase III randomized trial (ZEAL study) is evaluating the efficacy and safety of subsequent Zevalin versus observation in elderly patients with DLBCL in complete remission after first-line R-CHOP immunochemotherapy.

Novel approaches aimed at improving the efficacy of preparative regimens for ASCT incorporate the RIT at standard or escalated doses. In a Phase II study, <sup>90</sup>Y-ibritumomab-tiuxetan was successfully escalated, in combination with etoposide and cyclophosphamide, with good results and tolerance.<sup>[63]</sup>

At last, new drug categories are being investigated in Phase I-II studies and will soon find their more appropriate role in the therapy of DLBCL; these new drugs include antiangiogenetic agents such as bevacizumab and lenalidomide, and proteasome inhibitors such as bortezomib.<sup>[64]</sup>

## Table 1. Outcome of Diffuse Large B-cell Lymphoma According to aaIPI Score

Risk categories	No. of risk factors (aalPI score)	CR rate (%)	5-year RFS (%)	5-year OS (%)
Low	0	92	86	83
Low-intermediate	1	78	66	69
High-intermediate	2	57	53	46
High	3	46	58	32

aalPI = Age-adjusted International Prognostic Index; CR = Complete remission; OS = Overall survival; RFS = Relapse-free survival.

## Table 2. R-CHOP as Standard Therapy for Diffuse Large B-cell Lymphoma

Prognostic groups	Study	Programs
Patients aged <60 years; IPI: 0-1; stage II-IV, I bulky	MInT	R-CHOP21 × 6
Elderly patients (aged ≥60 years); all IPI groups	GELA	R-CHOP21 × 8
Elderly patients (aged 60-80 years); all IPI groups	RICOVER-60	R-CHOP14 × 6 (R × 8)
Elderly patients (aged ≥60 years); all IPI groups	US Intergroup E4494	R-CHOP × 6-8 without R maintenance or CHOP × 6-8 with R maintenance

GELA: Group d'Etude des Lymphomes de l'Adult; MInT: Mab-Thera International Trial; R-CHOP: Rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone.

## Table 3. Ongoing Phase III Studies in Diffuse Large B-cell Lymphoma

Groups	Risk categories	Programs
DSHNHL (FLYER)	Age <60 years, aalPI 0, no bulky	R-CHOP21 × 6 vs R-CHOP21 × 4 (R × 6)
DSHNHL (UNFOLDER)	Age <60 years, aalPI 1, bulky	R-CHOP21 × 6 vs R-CHOP14 × 6
DSHNHL	Age <60 years, aalPI 2-3	R-megaCHOEP × 4 vs R-CHOEP14 × 8
GELA	Age <65 years, aalPI 0	ACVBP14 vs R-ACVBP14 (22 weeks)
GELA	Age <65 years, aalPI 1	R-ACVBP14 (24 weeks) vs R-CHOP21 × 8
IIL (DLCL04)	Age <60 years, aalPI 2-3	R-CHOP14 × 8 vs R-megaCHOP14 × 6 vs R-CHOP14 × 4 + R-HDCT + ASCT vs R-megaCHOP14 × 4 + R-HDCT + ASCT (early FDG-PET evaluation)
HOVON (62)	Age <65 years, aalPI 0-1	R-iCHOP × 6 with R maintenance vs R-iCHOP × 6

NHL)		no R maintenance
HOVON (63 NHL)	Age <65 years, aa IPI 2-3	R-iCHOP × 6 vs R-iCHOP × 3 + R-HDCT × 2 + ASCT
US Intergroup S9704	Age <60 years, aaIPI 2-3	R-CHOP21 × 8 vs R-CHOP21 × 5 + ASCT (early FDG-PET evaluation)
GOELAM	Age <60 years, aaIPI 2-3	R-CHOP14 × 8 vs R-CEEP × 2 + HDMTX/Ara-C + ASCT
Nordic Cooperative Group	Age <60 years, aaIPI 2-3	R-CHOEP14 × 6 + HDMTX + HD Ara-C × 6 (early FDG-PET evaluation)
GITIL	Age <60 years, aaIPI 2-3	R-CHOP14 × 8 vs R-HDS
GELA	Age >65 years	R-CHOP21 × 8 vs R-CHOP14 × 8
DSHNHL RICOVER-60	Age >60 years	CHOP14 × 6 vs CHOP14 × 8 vs R-CHOP14 × 6 vs R-CHOP14 × 8
HOVON	Age >65 years	CHOP14 × 8 vs R-CHOP14 × 6 + CHOP14 × 2
CALGB	All patient groups	R-CHOP21 × 8 vs DA-EPOCH × 6-8
NCRI	All patient groups, stratification according to IPI and age: <60 vs ≥60 years	R-CHOP21 × 8 vs R-CHOP14 × 6 (R × 8)

aaIPI = Age-adjusted International Prognostic Index; ACVBP = Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; ASCT = Autologous stem cell transplantation; CALGB = Cancer and acute leukemia group B; CEEP = Cyclophosphamide, epirubicin, vindesine, prednisone; CHOEP = CHOP + etoposide; CHOP = Cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone; DSHNHL = German High-Grade Non-Hodgkin Lymphoma Study Group; FDGPET = Fluorine-18-fluorodeoxyglucose PET; GELA = Groupe d'Etude del Lymphome de l'Adulte; GEOLAM = Groupe Ouest est Leucémies Aiguës Myéloblastiques; GITIL = Gruppo Italiano Terapia Innovative nei Linfomi; HD Ara-C = High-dose cytarabine; HDCT = High-dose chemotherapy; HDMTX = High-dose methotrexate; HDS = High-dose sequential chemotherapy; HOVON = Dutch-Belgian Hemato-Oncology Cooperative Group; iCHOP = Intensified CHOP; IIL = Intergruppo Italiano Linfomi; NCRI = National Cancer Research Institute; R = Rituximab.

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## Sidebar: Executive Summary

### Heterogeneity of diffuse large B-cell lymphoma

- Diffuse large B-cell lymphomas (DLBCLs) may present with several morphological variants, including centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic and plasmoblastic.
- Gene-expression profiling studies define distinct subtypes: germinal center B-cell-like, activated B-cell-like and primary mediastinal lymphoma of thymic origin.

### Clinical & biologic prognostic factors

- The International Prognostic Index (IPI) is built on five clinical risk factors: age over 60 years, advanced clinical stage (III-IV), lactate dehydrogenase serum level higher than normal, Eastern Cooperative Oncology Group performance status higher than 1 and presence of more than one extranodal site of disease.
- IPI score correlates with response rate and survival (relapse-free and overall).
- Expression of the bcl-2 protein correlates with a poorer prognosis.
- Expression of the bcl-6 protein correlates with a better prognosis.
- The germinal center B-cell-like profile predicts better outcome compared with the activated B-cell-like profile; this has not been reproduced after the introduction of rituximab.

### Role of immunochemotherapy

- Cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) chemotherapy supplemented with the humanized anti-CD20 monoclonal antibody rituximab (R-CHOP), is the current standard therapy for diffuse large B-cell lymphoma.
- Dose-dense R-CHOP14 (every 2 weeks), with granulocyte-colony stimulating factor support, is being compared with R-CHOP21 (every 3 weeks) in patients aged over 60 years.
- Six or eight cycles of R-CHOP14 proved to be equivalent in elderly patients.
- Six cycles of R-CHOP21 is the current standard of therapy in young patients (age <60 years) with favorable IPI.
- The standard therapy for unfavorable IPI in young patients is yet to be established.
- Rituximab overcomes the chemoresistance correlated with the expression of bcl-2.

### Possible role for upfront autologous stem cell transplant

- In the pre-rituximab era, no overall superiority was demonstrated for high-dose chemotherapy followed by autologous stem cell transplant over conventional or intensified chemotherapy, except in patients with high-intermediate or high IPI (retrospective subgroup analysis).
- The addition of rituximab to chemotherapy might have changed the scenario; ongoing randomized trials are addressing this issue in young patients with an unfavorable IPI score.

### Disclaimer

No writing assistance was utilized in the production of this manuscript.

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