CLINICAL INVESTIGATION

Diffuse large B-cell lymphoma: update on therapy and prognosis

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The introduction of rituximab in combination with chemotherapy has substantially changed the outcome of patients with diffuse large B-cell lymphoma. This update will discuss the factors that improved our predictive capacity in these lymphomas and the results obtained by large clinical trials in first-line and salvage therapy. As far as first-line therapy is concerned, mature data are available for low-risk patients younger than 60 and for elderly patients; for patients older than 60 with unfavorable risk factors, conclusive data are still pending. Despite major advances in the first-line therapy, approximately half of the patients with diffuse large B-cell lymphoma experience treatment failure or refractoriness to first-line therapy. The standard therapy in these patients is high-dose chemotherapy followed by peripheral stem cell transplantation as hematologic rescue. Prior rituximab, as part of first-line therapy, does adversely influence the outcome of salvage therapy. New molecules and antibodies are being investigated in Phase I/II studies in patients who have relapsed or exhibit primary refractoriness and in those not eligible for peripheral stem cell transplantation. The new perspectives with these agents will be discussed.

Keywords: clinical trials • cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy • diffuse large B-cell lymphoma • novel agents • PET • prognostic factors • rituximab

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of adult B-cell lymphoma; the median age at diagnosis is 60–65 years and two thirds of patients present with advanced-stage disease [1].

The WHO classification defines several morphological variants; the immunophenotype constantly shows the presence of B-cell markers, notably the CD20, CD19 and CD22 antigens [2]. Gene expression-profile studies have identified at least three distinct molecular subtypes of DLBCL [3], one with a profile similar to that of normal germinal-center B cells (GCB subtype), one mimicking the activated peripheral-blood B cells (ABC subtype), while the third distinct subtype is representative of the primary mediastinal B-cell lymphoma. A small number of cases do not fit into any of these categories and have been defined as unclassifiable.

Clinical prognostic factors

At the beginning of the 1990s, an international effort was undertaken to correlate clinical variables with outcome in patients with untreated aggressive lymphomas (to which, DLBCL belong). Variables associated with a worse outcome were age over 60, advanced-stage disease (i.e., stage III–IV), elevated serum lactate dehydrogenase, Eastern Cooperative Oncology Group performance status >1 and involvement of two or more extranodal sites. An International Prognostic Index (IPI) was developed based on these five variables in patients treated with

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doxorubicin-containing regimens and four prognostic categories were defined, accordingly: low (0 or one factor), low-intermediate (two factors), high-intermediate (three factors) and high risk (four or five factors). An adjustment of the IPI score was subsequently developed for patients younger than 60 (age-adjusted IPI [aaIPI]), where adverse prognostic factors were advanced stage, elevated LDH and performance status >1. In this system, four distinct prognostic groups were identified (Table 1) [4].

A revision of IPI has been proposed after the introduction of rituximab (R-IPI), and it has demonstrated to retain its predictive capacity. The R-IPI is based on the same risk factors as IPI and identifies three prognostic groups with significantly different outcomes. Patients with no risk factors represent the 'very-good' prognostic category and demonstrate a long-term progression-free survival (PFS), higher than 90%. One or two risk factors set up a 'good' prognostic category, with 80% long-term PFS. More than two risk factors identify a 'poor-risk' group, with a long-term PFS and overall survival (OS) of approximately 50% (Table 2) [5]. Given the fact that neither IPI nor R-IPI stratify a risk group with less than 50% chances of long-term PFS, other predictors are needed to identify extremely high-risk patients, who may need alternative therapies. Gene-expression profiling seems to keep its predictive power in the rituximab era, as shown by Lenz and colleagues in a large series of patients [6]. The presence of c-myc rearrangement is a strong adverse prognostic factor in patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP); this molecular marker, together with age and IPI can be utilized to predict the clinical outcome in DLBCL. The poor prognosis of these patients is likely to reflect a synergistic effect of the c-myc rearrangement with other molecular deregulations including the expression of BCL-2 and BCL-6 [7].

Early restaging with PET (interim PET) has demonstrated encouraging results as a prognostic tool in DLBCL, but it requires further investigation.

First-line standard therapy & on-going clinical trials

For years, CHOP chemotherapy, administered every 21 days (CHOP21), has been the standard therapy for DLBCL, achieving a 3-year OS of 54% and a long-term OS rate above 50% [8]. In the attempt to improve the CHOP efficacy, some modifications to the classical scheme have been explored, in terms of both dose intensity and dose density. With regards to dose intensity, the doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) regimen, developed by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), demonstrated better results compared with CHOP, in terms of event-free survival (EFS) and OS in patients with poor prognosis, and the CHOP plus etoposide (CHOEP) regimen, developed by the German High-Grade non-Hodgkin's Lymphoma (DSHNHL) group, proved to be superior to CHOP in young patients with good prognosis [9,10]. As far as dose density is concerned, the 2 weeks based CHOP (CHOP14) regimen produced longer survival compared with CHOP21 in both young and elderly patients [10].

The therapeutic scenario in DLBCL was substantially changed by the introduction of rituximab, a murine anti-CD20 monoclonal antibody. The role of rituximab was first evaluated in elderly (>60 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. This superiority was evident in both favorable and unfavorable IPI groups and survival benefit was maintained over time; toxicity did not substantially increase, although a trend towards a higher risk of infections was observed after R-CHOP compared with CHOP [11]. The impact of adding rituximab to CHOP, in both young and elderly patients with DLBCL has been 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 patients treated with rituximab-containing regimens had an 18% absolute

Table 1. Outcome of diffuse large B-cell lymphoma according to the age-adjusted International Prognostic Index score.

Risk categories	No. of risk factors (aaIPI 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

aaIPI: Age-adjusted International Prognostic Index; CR: Complete remission; No.: Number; OS: Overall survival; RFS: Relapse-free survival.

Table 2. Outcome of diffuse large B-cell lymphoma according to the rituximab-International Prognostic Index score.

Risk categories	No. of risk factors (IPI score)	4-year PFS (%)	4-year OS (%)
Very Good	0	94	94
Good	1,2	80	79
Poor	3, 4, 5	53	55

IPI: International Prognostic Index; No.: Number; OS: Overall survival; PFS: Progression-free survival.

improvement in 2-year PFS and a 25% improvement in 2-year OS compared with those treated in the pre-rituximab era [12].

Young patients with favorable aaIPI

The Mab-Thera International Trial (MInT) has stated that in young (<60 years) patients with low-risk disease (aaIPI: 0–1), six cycles of R-CHOP21 are superior to CHOP21, in terms of EFS (79 vs 59%), and OS (93 vs 84%). In patients with an aaIPI score of 0 and no bulk, time-to-treatment failure and OS 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 [13,14]. According to these results, six cycles of R-CHOP21 may be considered the standard therapy in low-risk young patients with DLBCL. With regards to dose–intensity, the GELA group presented at the American Society of Hematology (ASH) 2010 meeting the results of the LNH03-2B trial that compared R-CHOP21 × eight cycles versus R-ACVBP14 × four cycles in patients with aaIPI1. R-ACVBP consisted of four induction courses given every 2 weeks: rituximab (375 mg/m^2), doxorubicin (75 mg/m^2), cyclophosphamide (1200 mg/m^2) on day 1, vindesine (2 mg/m^2) and bleomycin (10 mg) on day 1 and 5, prednisone (60 mg/m^2) from day 1–5, intrathecal methotrexate (15 mg) on day 2, G-CSF from day 6 to day 13. Patients then received a sequential consolidation therapy: two courses of methotrexate (3 g/m^2) plus leucovorin rescue, four courses of rituximab (375 mg/m^2), etoposide (300 mg/m^2) and ifosfamide (1500 mg/m^2) on day 1 and 2, courses of cytosine arabinoside (100 mg/m^2, subcutaneously) for 4 days; each consolidation course being administered at a 14-day interval. This study concluded that intensified immunochemotherapy with R-ACVBP significantly improved EFS (66.7 vs 80.9%), PFS (73.4 vs 86.8%), disease-free survival (80.3 vs 91.3%) and OS (83.8 vs 92.2%) compared with R-CHOP21, with manageable hematologic toxicity in younger patients with DLBCL [15]. However, the results of the R-CHOP21 arm in this trial were seemingly inferior to the results achieved with the same program in the MInT trial for patients with the same prognosis (EFS: 67 vs 80%; PFS: 73 vs 86%; OS: 84 vs 90%), and the results of the R-ACVBP arm were similar in terms of OS to those achieved with R-CHOP21 in the MInT trial.

On-going trials of the DSHNHL are now dealing separately with the very favorable (i.e., aaIPI: 0, no bulk) and favorable risk subgroups (i.e., aaIPI: 1 and/or bulk). In the very low-risk category, the DSHNHL-FLYER trial is comparing six courses of R-CHOP21 versus 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 versus six courses of R-CHOP21.

Young patients with unfavorable aaIPI

No standard therapy has yet been established for patients younger than 60, with unfavorable prognosis (i.e., aaIPI: 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. A GELA study showed an advantage of high-dose chemotherapy with ASCT for patients with IPI scores of 2–3, while a GOELAM study produced the same results in intermediate-high risk patients [16,17]. However, other studies did not demonstrate a survival benefit between high-dose chemotherapy and standard-dose therapy [18,19]. 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 nonrandomized 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 [20,21]; the reported PFS rates, however, do not exceed 60%, indicating the need for a more intensive approach such as intensified chemoimmunotherapy with rituximab-containing high-dose chemotherapy followed by ASCT.

Several trials are underway in young patients with unfavorable IPI scores and most of them do randomize dose-dense immunochemotherapy versus up-front rituximab-containing high-dose chemotherapy with ASCT. The DSHNHL group has compared eight cycles of dose-dense R-CHOEP14 with progressively dose-escalated R-CHOEP followed by repeated stem cell transplants to achieve maximal dose intensity. The dose-escalated R-CHOEP arm has been prematurely closed for unacceptable toxicity. A Phase III randomized study sponsored by the Intergruppo Italiano Linfomi (IIL-DLCL04 trial), compared R-dose-dense chemotherapy (eight courses of R-CHOP14 or six courses of R-megaCHOP14) with the same immunochemotherapy (four courses of R-CHOP14 or R-megaCHOP14) followed by dose intensification with two cycles of mitoxantrone 8 mg/m^2/day for 3 days, cytarabine 2000 mg/m^2/12h for 3 days and dexamethasone 4 mg/m^2/day for 3 days (R-MAD) and carmustine, etoposide, cytarabine and melphalan (BEAM) as a conditioning regimen for ASCT. Patient accrual has been completed and data analysis is underway. In addition, 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. Other Phase III randomized studies evaluating up-front rituximab plus high-dose chemotherapy with ASCT include the US Intergroup S9704 trial comparing eight cycles of R-CHOP21 versus five cycles of R-CHOP21 plus ASCT. At the ASH 2010 meeting, the GOELAM presented the results of the 075 trial: in this trial, patients were randomised at diagnosis between R-CHOP14 (eight consecutive courses if a response was observed after the first four courses) and two cycles of cyclophosphamide, epirubicin, vindesine and prednisone (R-CEEP) followed by high-dose methotrexate/cytarabine and ASCT. Patients not achieving at least a partial response at the intermediate evaluation underwent salvage chemotherapy followed by ASCT. No significant difference between the two arms was observed in terms of overall response rate (ORR; 78 vs 71%) and the paper does not recommend high-dose chemotherapy as first-line treatment for young adults [22].

Elderly patients

The results of the RICOVER-60 trial have recently been published; 1222 elderly patients (aged 61–80 years) were randomly assigned to six or eight cycles of CHOP14, with or without rituximab. Involved-field radiotherapy (36 Gy) was mandatory for patients with initial bulk (>7.5 cm) and/or extranodal disease. Results indicate that six cycles of CHOP14 plus eight doses of rituximab significantly improved EFS, PFS and OS compared with six cycles of CHOP14, and that eight cycles of therapy were not better than six [23]. These results suggest that six cycles of R-CHOP14, with the G-CSF support, may be considered the standard therapy for elderly patients in all IPI categories. However, there is no general agreement on the superiority of dose-dense R-CHOP14 over R-CHOP21, and further randomized trials are ongoing to compare these two regimens. Table 3 reports the most important randomized ongoing clinical trials.

Therapy for relapsed or refractory patients

Despite major advances in the first-line therapy with the introduction of rituximab and dose-dense regimens, approximately half of the patients with DLBCL experience early relapse or refractoriness to first-line chemotherapy. The outcome in these categories of patients is severe, with a median survival shorter than 12 months with conventional salvage chemotherapy. The initial approach to relapsed or refractory disease is to determine whether the patient is a potential candidate for high-dose therapy followed by ASCT. In 1995, the PARMA trial evaluated salvage chemotherapy with the platinum and cytarabine-based regimen, dexamethasone, cisplatin plus cytarabine (DHAP) versus DHAP combined with ASCT [24]. Both EFS and OS were significantly longer in the transplant group versus the chemotherapy alone group. Based on these results, ASCT has become the standard of care for younger patients with relapsed or primary refractory aggressive lymphoma [25].

There are further questions regarding the best salvage chemotherapy regimen, the efficacy of rituximab in patients previously treated with this antibody and the role of maintenance with rituximab after ASCT. The CORAL study randomized patients with refractory or relapsed DLBCL to receive rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) or rituximab plus DHAP (R-DHAP). The whole series ORR was 63%, with 38% of patients achieving a complete remission (CR). No difference between R-ICE and R-DHAP was observed in term of overall response (63.5 vs 62.8%), 3-year EFS (26 vs 35%; p = 0.6) and OS (47 vs 51%; p = 0.5) [26]. Moreover, the CORAL study results have clearly indicated that the response rate to salvage immunochemotherapy was affected by prior treatment with rituximab; indeed, the ORR in patients not previously given rituximab was 87 versus 51% for those who had prior immunotherapy (p < 0.0001).

The Bio-CORAL study presented at the 2010 ASH meeting showed that patients with a GC B cell-like DLBCL subtype treated with R-DHAP have a better 2-year PFS (64 ± 7%) compared with those with GC

Table 3. Ongoing Phase III studies in diffuse large B-cell lymphoma.

Groups	Risk categories	Outline
DSHNHL (FLYER)	Age <60, aaIPI: 0, no bulk	R-CHOP21 × 6 vs R-CHOP21 × 4 (R x 6)
DSHNHL (UNFOLDER)	Age <60, aaIPI: 1, bulk	R-CHOP21 × 6 vs R-CHOP14 × 6
IIL-DLCL04	Age <60, aaIPI: 2–3	R-CHOP14 × 8 vs R-megaCHOP14 × 6 vs R-CHOP14 × 4 + R-HDCT + ASCT vs R-megaCHOP14 × 4 + R-HDCT + ASCT
HOVON (63 NHL)	Age <65 aaIPI: 2–3	R-iCHOP × 6 vs R-iCHOP × 3 + R-HDCT × 2 + ASCT
US Intergroup S9704	Age <60, aaIPI: 2–3	R-CHOP21 × 8 vs R-CHOP21 × 5 + ASCT
Nordic	Age <60, aaIPI: 2–3	R-CHOEP14 × 6 + HDMTX + HDAra-C × 6
GELA LNH 07–3B	Age <60; aaIPI: 2–3	R-CHOP14 vs R-ACVBP14
GITIL	Age <60, aaIPI: 2–3	R-CHOP14 × 8 vs R-HDS
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	R-CHOP21 × 8 vs R-CHOP14 × 6 (R x 8)

aaIPI: age-adjusted IPI; ACVBP14: Hydroxydoxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone every 14 days; ASCT: Autologous stem cell transplantation; CALGB: Cancer and Acute Leukaemia Group B; CHOEP: CHOP and etoposide; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; DA-EPOCH: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; DSHNHL: German High-Grade non-Hodgkin Lymphoma Study Group; FLYER: Favorable low-risk young patients: equivalency of rituximab; GELA: Groupe d'Etude des Lymphomes de l'Adulte; GITIL: Gruppo Italiano Terapia Innovative nei Linfomi; HDAra-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; IPI: International Prognostic Index; NCRI: National Cancer Research Institute; R: Rituximab; R-CHOP14: Rituximab with CHOP every 14 days; R-CHOP21: Rituximab with CHOP every 21 days.

B cell-like DLBCL treated with R-ICE (42 ± 7%) and compared with patients with ABC B cell-like DLBCL treated either with R-DHAP (35 ± 7%) or R-ICE (45% ± 7%; p = 0.04) [27].

Salvage therapy with new biologic molecules and/or new antibodies should be considered in patients not eligible for autologus transplantation owing to age or comorbidity.

Predictive value of interim PET

Fluoro-2-deoxy-D-glucose PET has widely been introduced as a tool for 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 EFS (82 vs. 43%) and OS (90 vs. 61%) compared with those remaining positive at the interim-PET analysis [28]. 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 an aaIPI of 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, shift to early salvage with the CORAL protocol. The crucial problem with interim-PET analysis in DLBCL 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 plus ASCT), 36% of patients were positive at the interim-PET analysis (after four cycles of R-CHOP14), with only 13% of them having a positive biopsy for residual disease. The positive predictive value of interim PET in this experience was lower than 20% [29]. In another series, positive interim PET after two cycles of R-CHOP was not predictive, whereas end of therapy PET strongly correlated with PFS [30]. This implies that interpretation criteria for interim PET needs to be standardised and that, at the moment, only the negative predictive value of interim PET seems to be clinically applicable.

Novel agents

The most important novel agents being tested as salvage therapy for patients with relapsing or resistant large B-cell lymphoma are listed in Table 4.

The radio-immunoconjugate ^{90}Y-ibritumomab tiuxetan (Zevalin®) proved to be effective against large B-cell lymphoma, with an ORR of 52%, in a cohort of relapsed/refractory elderly patients with DLBCL pretreated with rituximab and considered uneligible for ASCT [31]. These results supported further studies on ^{90}Y-ibritumomab tiuxetan activity in elderly/frail patients. In a recent Phase II trial, untreated elderly patients with DLBCL received six courses of CHOP and were further consolidated with ^{90}Y-ibritumomab tiuxetan [32]. An ongoing Phase III randomized trial, termed ZEAL study, is evaluating the efficacy and safety of subsequent ^{90}Y-ibritumomab tiuxetan versus observation in elderly patients with DLBCL in CR after first-line R-CHOP immunochemotherapy.

Another group of agents is represented by the thalidomide derivative lenalidomide, which exerts its effect via the activation of the innate or adoptive immune system, the modification of the cytokine microenvironment and the angiogenesis inhibition. The efficacy and safety of lenalidomide has been evaluated in patients with relapsed/refractory aggressive lymphoma (DLBCL and mantle cell lymphoma) by the NHL-003 Phase II study. In a group of 73 patients with DLBCL, the ORR was 29%, with a CR rate of 4%. The median duration of response was 7 months and the most common grade 3/4 adverse events were neutropenia (31%) and thrombocytopenia (15%). The NHL-003 data suggest that patients with the ABC subtype of DLBCL are likely to have the most durable response to lenalidomide; a Phase III trial is evaluating lenalidomide in patients with relapsed/refractory DLBCL according to their immunohistochemical profile [33].

Table 4. Novel agents in diffuse large B-cell lymphoma.

Drug	ORR (%)	CR (%)	Ref.
^{90}Y-ibritumomab tiuxetan	19	12	[31]
	100	95	[32]
Lenalidomide	29	4	[33]
Bortezomib	13 (GCB) 83 (ABC)	6.5 (GCB) 41.5 (ABC)	[34]
Panobinostat	90	68	[36]
Vorinostat	5.6	5.5	[38]
Bevacizumab	–	–	[43]
Fostamatinib	21.7	4.3	[44]

ABC: Activated peripheral-blood B cells; CR: Complete remission; GCB: Germinal-center B cells; ORR: Overall response rate.

The proteasome inhibitor bortezomib, known for its activity against multiple myeloma and mantle cell lymphoma, is now being investigated as salvage treatment for DLBCL. A recent study showed that bortezomib can enhance the activity of chemotherapy in the ABC subtype of DLBCL [34]. The role of bortezomib in association with R-CHOP21 was evaluated in untreated patients, as well [35]. This regimen was well tolerated, and the most frequently reported adverse event was the sensory peripheral neuropathy (55%). The ORR was 90% and the CR rate was 68%; the estimated 2-year PFS was 72%. Provisional results suggest that bortezomib may enhance the activity of chemotherapy in the ABC subtype of DLBCL.

Another class of agents active in DLBCL is the histone deacetylase inhibitors. These molecules are potent antiproliferative agents, which cause cell-cycle arrest and apoptosis and may have additive or synergistic effects with antiproliferative drugs. Panobinostat and vorinostat are the compounds currently being investigated in Phase I/II studies [36–38].

Elevated serum levels of VEGF correlate with worse prognosis in patients with lymphoma [39–41]. Bevacizumab, a recombinant, humanized, monoclonal antibody against VEGF, has been added to R-CHOP and compared, in a Phase III randomized study, to R-CHOP alone [42]. The addition of bevacizumab to standard R-CHOP did not significantly improve efficacy; the toxicity, on the contrary, increased in the bevacizumab arm, with a significantly higher risk of congestive cardiomiopathy and of gastrointestinal perforation [43].

The B-cell receptor (BCR) signaling pathway is another promising target for novel agents against DLBCL. Constitutive BCR signaling is critical for survival and proliferation of both murine and human B-cell lymphomas. The primary effect of BCR signaling appears to be the activation of Syk, which leads to several downstream events promoting cell survival. R406 is a potent and selective inhibitor of Syk and fostamatinib disodium is a prodrug of R406, available in an oral formulation. In a Phase II study, a twice daily administration of fostamatinib significantly reduced Syk activity, with no adverse effects on immunity and hemostasis and a 21% ORR [44].

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Executive summary

Clinical & biologic prognostic factors

- The International Prognostic Index (IPI) is built on five clinical risk factors for diffuse large B-cell lymphoma: age over 60, advanced clinical stage (i.e., stage III-IV), lactate dehydrogenase serum level higher than normal, Eastern Cooperative Oncology Group performance status >1 and the presence of more than one extranodal site of disease. The IPI score correlates with response rate and survival (relapse-free and overall).
- A revision of IPI has been proposed after the introduction of rituximab , and showed to retain its predictive capacity. The so called R-IPI is based on the same risk factors as IPI and identifies three prognostic groups with significantly different outcomes.
- At the moment, only the negative predictive value of interim PET is clinically applicable.

The role of immunochemotherapy in first-line therapy

- Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy (R-CHOP) is the standard therapy for diffuse large B-cell lymphoma.
- Six cycles of R-CHOP every 21 days is the standard therapy in young patients (<60 years) with favorable age-adjusted IPI score (i.e., IPI score: 0–1).
- The standard therapy for young patients with unfavorable age-adjusted IPI scores (i.e., IPI score: 2–3) is yet to be established.
- Six cycles of R-CHOP every 14 days, with G-CSF support, is the standard therapy for elderly patients in all IPI categories.

Salvage therapy

- The standard salvage therapy is high-dose chemotherapy followed by peripheral stem cell transplantation. Prior rituximab, as part of first-line therapy, does adversely influence the outcome of salvage therapy.
- Salvage therapy with new biologic molecules and/or new antibodies should be considered in patients not eligible to autologus transplantation for age or comorbidity.

Novel agents

- New biologic molecules and new antibodies are being investigated in Phase I–II studies; encouraging results have been demonstrated by the radio-immunoconjugate ^{90}Y-ibritumomab tiuxetan, lenalidomide, the proteasome inhibitor bortezomib, histone deacetylase inhibitors and monoclonal antibodies against VEGF and Syk inhibitors.

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