



Management of nodal diffuse large B-cell lymphomas: practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

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The Italian Society of Hematology (SIE) and two affiliate societies (SIES and GITMO) commissioned a project to develop clinical practice guidelines for the treatment of nodal diffuse large B-cell non Hodgkin lymphomas (DLBCL). Key questions clinically relevant to the management of patients with nodal DLBCL were formulated by an Advisory Committee (AC) and approved by an Expert Panel (EP) composed of eight senior hematologists. After a comprehensive and systematic literature review, the EP formulated therapy recommendations and graded them according to the supporting evidence. An explicit approach to consensus methodologies was used for evidence interpretation and for producing recommendations in the absence of strong evidence. The EP formulated recommendations on which first-line therapy to choose in patients with nodal DLBCL. Patients of all ages, with stage I-II disease and no adverse prognostic factors should receive abbreviated chemotherapy with an anthracycline-containing regimen plus involved field radiotherapy (35-40 Gy). Patients with stage I-III disease and at least one adverse prognostic factor, or with stage III-IV disease, should receive frontline chemoinmunotherapy with CHOP, CHOP-like or third-generation chemotherapy plus rituximab. Recommendations on stem cell transplantation and on which therapy to adopt for refractory or relapsed patients were also formulated.

Key words: non-Hodgkin's lymphoma, clinical practice guidelines, systematic review, rituximab, chemotherapy.

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The annual incidence of large B-cell lymphoma (DLBCL) is 2-8 cases per 100,000 inhabitants per year.¹ This disease accounts for 20 to 40 % of cases of non-Hodgkin's lymphoma (NHL),¹⁻³ and the median overall survival (OS) of patients with DLBCL is shorter than 5 years.⁴ Several therapeutic innovations have been recently introduced, and subjective integration of older and new pieces of evidence may lead to conflicting conclusions and a large variation in clinical practice. In order to select the best available treatments, avoiding inappropriate ones, the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES) and the Italian Group for Bone Marrow Transplantation (GITMO) supported the development of clinical practice guidelines focusing on the therapy of nodal DLBCL. The guidelines are intended to help hematologists, oncologists and internists who care for patients with lymphoma.

Design and Methods

Organization and design

The organization and design of this project have been reported in a previous paper on guidelines for the management of nodal indolent non-Hodgkin lymphomas.⁵ The first search of evidence databases was performed on 20th July 2003, but updated

searches of the literature were continued during the project. The full reference list (including the abstracts of full papers) is available on request from marchettim@smatteo.pv.it. The grading system chosen for the present guidelines is the one developed by the Scottish Intercollegiate Guideline Network (SIGN).⁶ The recommendations are, therefore, graded class A if supported by consistent and applicable level 1 evidence (at least one level 1++ trial or some consistent level 1+ trials), class B if evidence was derived from consistent results of level 2++ studies or was extrapolated from level 1+/1++ trials, class C if supported by grade 2+ studies that could be applied directly to the object population and provided consistent results, or level 1++ studies from different populations (translated evidence), and grade D when supported by poor quality evidence or evidence extrapolated from grade 2+ studies, and thus sustained mainly by experts' opinion. The draft guidelines were reviewed by an external Panel of expert radiotherapists and by the presidents of the SIE, SIES and GITMO scientific societies. Updating of the present guidelines is expected in 2008.

Definitions

During the first consensus conference, the Expert Panel (EP) agreed to address DLBCL, defined according to the WHO classification

Table 1. Response criteria for lymphomas.

Response Category	Lymph Nodes	Other sites	Bone Marrow
Complete Response (CR)	Regression to ≤ 1.5 cm GTD in nodes >1.5 cm before therapy and to ≤ 1 cm GTD (or by more of 75% SPD) in nodes 1.1-1.5 cm before therapy	Regression or maintenance of normal size	Normal
Complete Response undefined (CRu)	Possible residual nodes >1.5 cm GTD but with a SPD regression by $>75\%$	Regression or maintenance of normal size	Normal or indeterminate (increased number or size of aggregates without cytological or architectural atypia)
Partial Response (PR)	$>50\%$ decrease in SPD of the 6 largest nodes or nodal masses and no increase in size of other nodes	Spleen and liver: no increase in size; regression by $>50\%$ in nodules. No new sites of disease.	Irrelevant
Relapse (for patients with CR or CRu at the end of therapy)	Appearance of any new nodes and/or increase by $>50\%$ in the size of previously involved nodes	Appearance of any new lesion and/or increase by $\geq 50\%$ in the size of previously involved sites	Appearance or reappearance of involvement
Progression (for patients on therapy or with PR or nonresponders at the end of therapy)	$>50\%$ increase from nadir in SPD of any previously abnormal node	Appearance of any new lesion	Appearance or reappearance of involvement

GTD: greatest transverse diameter; SPD: sum of the products of the greatest diameter (adapted from: Cheson et al.).⁹

of mature peripheral B-cell neoplasms, excluding primarily mediastinal lymphomas. HIV-related lymphomas and Richter's syndrome were excluded from the target domain of the present guidelines. The EP also agreed on the use of the Ann Arbor staging system as modified by the Cotswolds meeting,⁷ and on the use of the International Prognostic Index (IPI).⁸ Standard definitions for response were adopted (Table 1).⁹ An operational definition of elderly patients was considered that takes into account not only age but also performance status and comorbidities of the patients.

Results

First-line therapy for stage I-II disease

The EP addressed two main issues concerning the optimal therapeutic strategy for localized DLBCL: should patients receive radiotherapy (RT), and should young patients receive more aggressive chemotherapy than the standard CHOP regimen? Evidence on the efficacy of, extended field RT derived from a detailed retrospective analysis.¹⁰ of 451 adult patients (243 with histological high-grade disease) initially treated with RT alone; the complete remission (CR) rate was 84%. In those patients under 60 years of age at diagnosis, the overall cause-specific survival at 10 years was 80%. Evidence on greater efficacy of RT plus chemotherapy with respect to RT alone was derived from one randomized trial (level 1+).¹¹ From 1974 to 1978, 73 patients were treated with RT alone or RT plus adjuvant chemotherapy with vincristine, streptonigrin, cyclophosphamide and prednisone. With a median follow-up of 5 years, 54% of patients in the RT group had relapsed versus only 10% in the RT plus chemotherapy group ($p < 0.01$). There was no statistical difference in the OS, but 13/14 deaths in the radiotherapy group versus only 3/12 in the radiotherapy plus chemotherapy group were due to progressive disease. Evidence on the

greater efficacy of chemoradiotherapy with respect to chemotherapy alone was derived from two randomized trials.^{12,13} The SWOG study enrolled patients with intermediate or high grade NHL. Two hundred patients were randomly assigned to receive three courses of CHOP plus radiotherapy or CHOP alone.¹² Patients treated with chemoradiotherapy had significantly better progression-free survival (PFS) ($p = 0.03$) and OS ($p = 0.02$) than had patients treated with chemotherapy alone. The 5-year estimates of PFS and OS for patients receiving chemotherapy plus RT and for patients receiving chemotherapy alone were 77% and 64%, respectively, and 82% and 72%, respectively. Life-threatening toxic effects of any type were seen in 61 of 200 patients treated with CHOP plus RT and in 80 of 201 patients treated with CHOP alone ($p = 0.06$). From 1984 to 1992, an ECOG study enrolled adult patients with stage I and II diffuse aggressive lymphoma in complete remission after eight cycles of CHOP.¹³ Patients were randomly assigned to 30 Gy involved-field RT or observation. Among 172 complete remission patients, the 6-year disease-free survival (DFS) was 73% in the low-dose RT group versus 56% in the group assigned to observation ($p = 0.05$). Failure-free survival (FFS) and time to progression (TTP) were also marginally better in the RT group, although no survival benefit was observed. Moreover, only 43% of the 399 patients initially registered actually received RT or observation. In the long term analysis of the SWOG trial, PFS and OS of chemo-radiotherapy and chemotherapy overlapped,¹⁴ and in the as-treatment analysis of the ECOG trial, the survival benefit provided by chemo-radiotherapy was no longer statistically significant. The results of the two above mentioned randomized trials were confirmed by observational non-controlled studies documenting that an abbreviated course of doxorubicin-based chemotherapy associated with RT limited hematologic and cardiac toxicities and drop-outs, while achieving an OS of more than

60% and a PFS of more than 70% at 10 years (level 2-/2++). Nevertheless, the need for RT has been questioned by two randomized trials by the GELA group; one trial was in young individuals, the other in elderly patients.^{15,16} In the first one, it was found that younger patients with low-risk localized lymphoma had a longer survival after dose-dense chemotherapy followed by consolidation chemotherapy, as compared with chemo-radiotherapy. In the second trial, 528 elderly patients with localized good prognosis (IPI 0) aggressive lymphoma were randomized to receive four courses of CHOP alone, or the same regimen followed by 40 Gy involved field (IF)RT. With a median follow-up of 49 months, chemotherapy alone was as effective as the combined treatment: the 5-year EFS and 5-year OS were 66% and 76% with CHOP alone as compared to 61% and 67%, respectively, for CHOP plus involved field RT. In patients over 69 years old, OS was better in those who were not given RT.

The EP discussed that most of the differences among studies could have resulted from different inclusion criteria and broad application of the term *limited* or *localized* for early stage disease. The EP concluded that the IPI score allows identification of patients with different prognoses also among those with stage I and II aggressive lymphomas, and patients with very limited disease (IPI score =0) have a good prognosis with a 10-year OS from 87% to 95% whether they are treated with an abbreviated course of doxorubicin-based chemotherapy followed by RT or with chemotherapy alone. Although dose-dense chemotherapy was shown to be effective in these patients and the number of fatal second cancers in the two groups of the GELA trial was not significantly different, the EP deemed that the risk of toxicity due to dose-dense chemotherapy needs to be accurately balanced against the potential benefits. Therefore, the EP judged that dose-dense chemotherapy could not be recommended in very limited stages of aggressive NHL.

Recommendations

Patients of all ages with stage I-II DLBCL and no adverse prognostic factors, i.e. non-bulky disease and IPI prognostic index equal to 0 (normal LDH serum levels, ECOG performance status < 2) should receive abbreviated chemotherapy with an anthracycline-containing regimen plus involved field RT (35-40 Gy) or a full course of chemotherapy alone [grade C]. Patients with stage I-II disease and at least one adverse prognostic factor (bulky disease, elevated LDH, performance status ECOG >1) should be treated according to the recommendations for stage III-IV disease [grade D].

First-line therapy for stage III-IV disease

A randomized trial conducted in elderly patients (60-69 years) with poor-prognosis aggressive non-Hodgkin's lymphoma showed that increased anthracycline and cyclophosphamide doses with interval reduction (ACVBP regimen) produced better 5-year EFS rates and OS than did standard CHOP chemotherapy.¹⁷ A dose-finding study,¹⁸ and two randomized studies^{19,20} tested the superiority of 2-weekly or 3-weekly CHOP chemotherapy with or without etoposide for patients

with aggressive lymphomas. In patients aged 61 to 75 years complete remission rates were 60.1% (CHOP-21), 70.0% (CHOEP-21), 76.1% (CHOP-14), and 71.6% (CHOEP-14). Five-year EFS rates and OS rates were 32.5% and 40.6%, respectively, for CHOP-21 and 43.8% and 53.3%, respectively, for CHOP-14. These studies provided evidence that CHOEP should be the preferred chemotherapy regimen for young patients with good-prognosis aggressive lymphoma, while due to its favorable efficacy and toxicity profile, CHOP-14 should be considered for patients aged 60 or older. Evidence that the association of chemotherapy and rituximab, i.e. chemoimmunotherapy, improved OS derived from one randomized trial.²¹ In older patients, the GELA NHL 98.5 randomized trial (level 1++) showed that the administration of rituximab, 375 mg/m² on day 1 of each cycle alongside standard CHOP chemotherapy (R-CHOP), i.e. 8 cycles every 21 days, reduced the risk of death by 36% and increased 2-year OS by 19% compared to CHOP alone. R-CHOP significantly improved EFS rates in both low and high risk patients and in bcl-2-positive patients, potentially overcoming the impact of this negative prognostic factor.²² These results were recently confirmed in an updated report with a 5-year median follow-up.²³ The EP was quite confident that the efficacy of chemoimmunotherapy is preserved in patients over 80 years of age who are eligible chemotherapy, since rituximab did not increase the overall toxicity of treatment. The efficacy of chemoimmunotherapy in both elderly and young patients has been recently confirmed by a large population-based prospective study (level 2++).²⁴ By comparing patients' survival before and after rituximab introduction into clinical practice, the British Columbia Cancer Agency observed that 2-year OS improved from 53% to 77% ($p=0.0001$) and 2-year PFS increased from 52% to 71%. In the elderly (>60 yrs) OS improved from 40% to 67% and PFS from 44% to 67%. In the young, OS improved from 69% to 87% and PFS increased by 10% ($p=n.s.$). Indeed, no difference in outcomes between young and old patients receiving chemoimmunotherapy was detected in a phase II study.²⁵ Evidence of the efficacy of chemoimmunotherapy in patients younger than 60 years was also derived from a partially reported randomized trial: the MabThera International Trial enrolled 820 patients aged less than 60 years and with an IPI score 0-1 (low risk) and administered rituximab every 21 days irrespective of chemotherapy scheduling, which included third-generation chemotherapy regimens, CHOP and CHOP-like chemotherapy.²⁶ However, direct evidence of the benefit of chemoimmunotherapy in young patients at high risk (IPI score 2-3) is still lacking.

The evidence on the use of rituximab as a single agent was translated from data on rituximab monotherapy in relapsed patients. The drug, administered at the dose of 375 mg/m² weekly for 4 weeks produced responses (mostly partial responses) in 30-40% of the patients in this setting. Maintenance rituximab after first-line chemoimmunotherapy is still under investigation. The EP judged that evidence was too scarce to recommend rituximab as a maintenance regimen.

High-dose chemotherapy with autologous stem cell rescue (HDT/autoSCT) was expected to improve chemotherapy outcomes in high-risk DLBCL patients. Indeed, in some clinical trials the survival curve after early HDT/autoSCT (i.e. first CR) proved superior to that after conventional chemotherapy, indicating the potential of this treatment to eradicate the disease. These observations are in contrast with those of two meta-analyses (level 1+) of up to 11 randomized trials,^{27,28} which showed a similar OS in patients receiving first-line HDT/autoSCT or standard chemotherapy. The significant heterogeneity among the studies, due to different study designs and treatment strategies, however, made the meta-analytic process itself poorly robust. Indeed, the studies in which the HDT/autoSCT arm had fewer than 25% drop-outs provided a significant reduction of mortality (OR 0.44, $p=0.01$). Some studies employing upfront high-dose sequential chemotherapy (HDS) reported a significant improvement in OS. However, in a recent trial by the Intergruppo Italiano Linfomi, this strategy did not improve the outcome in IPI 2-3 patients compared to dose-dense chemotherapy.²⁹ The EP judged that the evidence supporting the superiority of HDT/autoSCT over conventional chemotherapy is still too scarce and heterogeneous for a universal recommendation of first-line HDT/autoSCT. Moreover, chemoimmunotherapy greatly improved the long-term outcomes of patients with DLBCL and ongoing randomized studies are comparing chemoimmunotherapy with HDT/autoSCT in first-line therapy for DLBCL. The EP therefore recommended that non-elderly, high-risk patients may be selected for a frontline HDT/autoSCT strategy according to approved clinical protocols. The EP deemed it advisable that full debulking should precede HDT/SCT, since shortened induction is probably associated with worse outcomes after HDT/SCT.²³

An old randomized study prospectively compared involved field RT consolidation with no consolidation in 155 patients with a CR after CHOP-bleomycin chemotherapy (level 1-).³⁰ Involved field RT increased 5-year PFS from 35% to 72% and OS from 55% to 81%. These results were confirmed by non-randomized prospective (level 2+) and retrospective (level 2-) studies. RT doses ranged from 30 Gy to 53 Gy in the various studies, and was 45 Gy in the randomized study.³⁰ However, the EP judged it worth recommending a lower RT dose, in order to limit long-term occurrence of secondary cancers, being confident that the efficacy of consolidation involved field RT was preserved also at the 30-36 Gy dose. However, no well designed randomized studies properly addressed the issue of consolidation RT in advanced disease. Large co-operative groups, such as GELA, have been avoiding RT in their randomized trials for the past years in patients in CR with no evidence of inferior results.³¹ In the German studies, involved field RT (36 Gy) was delivered to the areas of initial bulky disease (>7.5 cm), irrespective of the results of chemotherapy.^{19,20} The interest in avoiding RT is to spare long-term toxicity such as cardiac or secondary malignancies in these patients. It has recently been shown that a persistent positive positron electron

tomography (PET) scan after front-line chemotherapy had a very poor prognostic impact on OS in patients with aggressive lymphoma. PET proved to have a high sensitivity and specificity for residual lymphoma masses and it might be argued that RT could be modulated based on the results of PET scans after chemotherapy. However, specific, randomized studies should be focused on this issue.

The risk of central nervous system (CNS) relapse in patients with intermediate-high grade NHL is about 5%, but a high-intermediate/high IPI score predicted a higher risk of CNS relapse. Chemoimmunotherapy did not reduce the risk of CNS relapses as compared with chemotherapy alone in a retrospective study.³² Therefore, the EP deemed it worth formulating a risk-adjusted recommendation for CNS prophylaxis in this subset of patients. Prophylaxis of CNS relapse should be given to patients with involvement of specific extranodal sites such as the testes, paranasal sinuses, hard palate, orbit, paravertebral masses and bone marrow. Patients with a high-intermediate/high IPI score, particularly reflecting the presence of a high level of LDH and involvement of more than one extranodal site,³³ are at much higher risk of CNS involvement than other patients and intrathecal prophylaxis should be suggested.

Recommendations

Patients with stage III-IV disease should receive frontline chemoimmunotherapy with CHOP, CHOP-like or third-generation chemotherapy plus rituximab [grade A/B]. The use of rituximab as first-line monotherapy is not recommended, except for patients with stage III-IV disease who are, temporarily or definitely, ineligible for chemotherapy [grade C]. Patients with an intermediate-high/high IPI score and who are less than 65 years old may receive a frontline HDT/autoSCT, but only within an approved study protocol. Patients enrolled into an HDT/autoSCT program should receive non-abbreviated debulking treatment [grade B].

Frontline allogeneic SCT is not recommended for any patient [grade C].

Patients with stage III-IV disease and bulky disease at diagnosis may receive consolidation involved field RT (30-36 Gy) to the sites of bulky disease [grade C].

Prophylaxis of CNS relapse should be performed in patients with involvement of specific extranodal sites such as the testes, paranasal sinuses, hard palate, orbit, paravertebral masses and bone marrow [grade B].

Prophylaxis of CNS relapse should also be used in patients presenting with a high-intermediate /high IPI score, particularly reflecting the presence of a high level of LDH and involvement of more than one extranodal site [grade C]. Prophylaxis should be performed with intrathecal injections of methotrexate at the beginning of each cycle of chemotherapy. The first intrathecal treatments should be administered within 14 days after the start of chemotherapy.

There is no role for maintenance therapy in patients in complete remission after first-line therapy outside a clinical trial.

Restaging and monitoring

PET has proven to have a high sensitivity and specificity for the detection of residual lymphoma masses and its diagnostic yield is greatly increased by associa-

tion with computed tomography scans. A longer PFS and lower relapse rate were found in PET-negative patients. Relapse rates ranged from 62.5% to 100% in PET-positive patients and from 3% to 17% in PET-negative ones.^{34,35} Preliminary data indicate that PET also has a better diagnostic yield over magnetic resonance imaging.³⁶ The EP considered the evidence of the diagnostic and prognostic role of PET in restaging DLBCL was consistent and recommended this test. PET scanning has a positive predictive value of 89% and a negative predictive value of 62% in assessing bone marrow involvement,³⁷ therefore, a negative PET scan is not considered sufficient for restaging patients with bone marrow involvement at diagnosis. Due to the heterogeneous populations enrolled into the studies assessing PET, including Hodgkin's lymphoma and NHL patients, the evidence supporting the prognostic yield of PET was down-scored to levels II and III.

Recommendations

Within 2 months after the end of first-line therapy (more than 3 months after completion of radiotherapy), patients with DLBCL should be restaged with CT and PET scans independently of the presence of a site of bulky disease at the time of diagnosis [grade D]. Bone marrow biopsy should be also performed in patients with bone marrow involvement at diagnosis [grade A].

All the patients with a CR-undefined and gastric, liver or intestinal involvement at diagnosis should have specific biopsies repeated if the surgical procedure is not severely harmful to the patient [grade B].

Patients with a complete remission should receive monitoring follow-up visits starting 3 months after restaging and repeated every 3 months for the first 24 months, then every 6 months for 36 months [grade D].

Second-line therapy

Before planning appropriate therapy, relapsed patients need to be adequately restaged.

Non-cross-reacting chemotherapy regimens, such as DHAP, ICE, MIME and high-dose regimens, such as HDS, proved to be effective in this subset of patients.^{38,39} Evidence on the efficacy of adding rituximab to reinduction chemotherapy was derived from non-controlled trials. Since prior administration of rituximab might impair CD20 expression on the surface of malignant cells, and since rituximab therapy requires CD20 expression by target cells for its efficacy, the EP recommended that the expression of this antigen should be assessed before including rituximab in any reinduction therapy.

After reinduction with non-cross-resistant chemotherapy, chemosensitive patients aged less than 65 years old who were free of severe comorbidity achieved a 5-years EFS of 35-60% after high-dose therapy and HDT/autoSCT, depending on prognostic factors at relapse (level 1++).⁴⁰ These data were confirmed by the ABMT registry (level 2++)⁴¹ and other longitudinal studies (level 2+). A pooled analysis of three phase II studies (level 2++)⁴² showed that the age-adjusted IPI score predicted outcome (logrank $p=0.001$) after HDT/autoSCT in this clinical setting: 150 refractory or

relapsed patients received ICE followed by the HDT/autoSCT program. Patients with primary refractory disease had a 4-year OS of 27% and a 4-year PFS of 20%, however, those who responded to ICE had a similar outcome as chemosensitive, relapsed patients.

High-dose chemotherapy followed by the HDT/autoSCT is also feasible in older patients, however, evidence is still scanty and the EP deemed it insufficient to formulate a specific recommendation; this strategy requires further investigation in controlled clinical studies.

The effect of *in vivo* purging on mobilization yield, time of engraftment and immune reconstitution in patients receiving *in vivo* purging is still being investigated. Rituximab cannot be recommended for maintenance after HDT/autoSCT, since no improvement in EFS was reported at 13 months of follow-up by the ongoing LNH 98-B3 GELA randomized trial.⁴³ Involved field RT to sites of bulky disease may be a useful consolidation therapy after HDT/autoSCT. Tandem HDT/autoSCT has been proposed as part of the initial therapy for DLBCL, however evidence is still scanty and non-comparative.

Patients who are not eligible for HDT/autoSCT may receive clinical benefit from radioimmunoconjugates (RIT) based on translated evidence from phase II studies including small subgroups of patients with aggressive NHL. The EP suggested that RIT should administered in the context of approved clinical protocols.

Patients who slowly achieve response to first-line therapy have a prognosis similar to that of patients with a PR, however, validation of this dynamic factor or incorporation into official response evaluation systems has not been judged consistent, yet. Therefore, the EP deemed it not to be appropriate to recommend different routine second-line therapies according to the response kinetics. Patients with IPI 2-3 and/or an early relapse (within 12 months) have a higher risk of relapse after HDT/SCT. Therefore, alternative experimental therapies may be offered to this subset of patients.

Relapsed patients who are not eligible for autoSCT and who are younger than 65 years can be considered for allogeneic stem cell transplantation (allo-SCT). Allo-SCT has been demonstrated to cure DLBCL in most of the patients who survive after the procedure: both relapse and survival curves reach a plateau 12-24 months after transplantation. However, the 5-year OS was reported to be 20-30% in refractory/relapsed DLBCL patients and no survival advantage was found between allo and autoSCT in a retrospective analysis of high-grade and DLBCL patients.

Recently, some evidence suggested that it may be possible to use the graft-versus-lymphoma (GVL) effect as a therapy for DLBCL without the need for myeloablative therapy, i.e. using reduced-intensity conditioning (RICT). Replacing high dose myeloablative therapy with a non-myeloablative conditioning regimen would allow treatment of those patients who are too old or medically unfit to qualify for conventional allografting. RICT has markedly reduced transplant-related mortality (TRM) (level 2).⁴⁴ However, TRM is still a main limitation to the use of allo-SCT and age remains a major determinant of TRM since patients over 50 years show

a 2-fold higher TRM even after RICT (level 2++ translated).⁴⁵ The potential benefits of RICT in patients with aggressive NHL were evaluated in 19 patients who received a low-intensity fludarabine-based conditioning regimen for allografting.⁴⁵ All patients engrafted. Transplant-related toxicity was moderate and four patients developed GVHD. At 37 months 40% of patients were disease-free. A recent review of the EBMT experience in 188 patients with lymphoma treated with RICT was less encouraging. Those patients with high-grade NHL had a poor outcome and the authors concluded that RICT may not be appropriate for DLBCL. Very promising results have recently been reported from two phase II studies with RICT in patients with various subtypes of NHL relapsing after auto-SCT. Extended use of allo-SCT in cases with little chance of disease control with auto SCT may be predicted from these reports.

Recommendations

Patients without a complete remission after first-line therapy and who are under 65 years old should receive non-cross-resistant regimens (e.g. ICE, DHAP, MIME, HDS) with or without rituximab [grade B]. Patients with a good performance status showing chemosensitivity to rescue chemotherapy should proceed to high-dose chemotherapy with HDT/SCT [grade A]. Patients chemoresistant to rescue chemotherapy should be enrolled into approved study protocols testing new drugs or experimental therapies (e.g. radioimmunoconjugates) or allogeneic SCT or receive supportive therapy [grade C].

Patients who do not achieve a complete remission after first-line therapy but aged more than 65 years should receive radioimmunoconjugates or non-cross resistant chemotherapy.

Patients with a disease relapse need to be restaged and CD20 positivity should be assessed before prescribing rituximab-containing therapy [grade D].

At first relapse, patients need to receive non-cross-resistant chemotherapy regimens (i.e. ICE, DHAP, MIME, HDS), with or without rituximab followed, in eligible patients, by high-dose chemotherapy and HDT/SCT [grade B]. Patients eligible for HDT/SCT include those aged < 65 years, with chemosensitive disease and a good performance status, without comorbidities and with good availability of autologous stem cells [grade A]. Eligible patients with an early relapse (<6 months from the end of first-line therapy) or an age-adjusted IPI score of 2-3 at the time of relapse are at high risk of relapse after HDT/SCT. The Panel advise enrollment of these patients into approved study protocols with experimental therapies [grade B].

Patients who are not eligible for HDT/SCT should be enrolled into approved study protocols of investigational therapies (e.g. radioimmunoconjugates, allogeneic SCT) or receive supportive therapy.

Mobilized peripheral blood stem cells should be preferred to bone marrow stem cells for HDT/SCT. Several procedures are available for mobilization of autologous stem cells: the combination of chemotherapy and granulocyte colony-stimulating factor may be preferred since this produces higher yields of progenitor cells than does the cytokine alone [grade C]. No data are available to support the use of ex-vivo purging for HDT/SCT and data reported so far are not sufficient to recommend the use of rituximab in vivo purging in all patients undergoing HDT/SCT. There are insufficient data to recommend the

use of double autologous transplantation. There are insufficient data to recommend the use of maintenance therapy after HDT/SCT.

Younger patients (< 50 years) who are candidates for allogeneic SCT should receive myeloablative conditioning. Patients aged over 50 years old should receive reduced-intensity conditioning [grade D].

Stem cells from either a sibling or an unrelated donor can be employed for allogeneic SCT [grade D]. The Panel suggested that total body irradiation may be incorporated into the conditioning regimen for myeloablative allogeneic SCT [grade D]. Fludarabine-containing conditioning regimens should be employed for reduced-intensity allogeneic SCT [grade C].

All patients with a bulky mass should receive involved field radiotherapy (30-36 Gy) to bulky sites after chemotherapy and high-dose therapy [grade B].

Discussion

In order to meet physicians' needs, the present guidelines are focused on the most relevant and specific issues in the complex clinical management of DLBCL. An extensive and systematic review of literature provided an up-to-date evidence base. However, in order to adhere to the quality standards for guideline production,⁴⁶ the SIES, SIE nd GITMO initiative of producing practice guidelines comprised interpretation and consensus on the evidence by members of an EP and a consensus phase for recommendations on key clinical issues not supported by good evidence.

Within this conceptual framework, the results of this project mostly adhered to the quality items produced by AGREE.⁴⁷ The only exceptions are that patients' views and preferences were seldom explicitly formulated into the recommendations, a pilot application of the guidelines has not been attempted and a monitoring or audit process has not been initiated. However, these guidelines have been externally reviewed by three expert radiotherapists and three senior hematologists, i.e. the presidents of the scientific societies endorsing the present guidelines.

The present guidelines are also aimed at supporting a rational use of novel technologies still under evaluation, such as monoclonal antibodies, reduced intensity conditioning and stem cell transplantation. The guidelines therefore cover a large domain, including the decision on how to approach first-line therapy, and the treatment of refractory and relapsed patients. Furthermore, different recommendations were formulated for diverse clinical scenarios, making the recommendations patient-specific. However, neither supportive therapy, i.e. hematopoietic growth factors, nor therapies for lymphoma-related complications, i.e. drugs for lymphoma-related autoimmune disorders, were specifically addressed by the present guidelines, since these issues belong to more general supportive care in the field of hemato-oncology. Recommendations on the prevention of tumor lysis syndrome were also left out of by the present guidelines because they are not specific to DLBCL. The present guidelines agree with all other guidelines on the recommendation for first-line chemoimmunotherapy for elder-

Table 2. Comparison among guidelines for first-line treatment of nodal diffuse large B-cell lymphomas.

	BCCA ⁴⁹	NCCN ⁵⁰	ESMO ⁵¹	ONCOGUIDE ⁵²	SIE, SIES, GITMO
Year	2002	2003	2002	2003	2005
Target	Malignant NHL	DLBCL	DLBCL	DLBCL	DLBCL
Country	Canada	US	Europe	Spain	Italy
Stage I-II non-bulky	CHOP x 3 + IFRT	In patients without adverse risk factors: CHOP 3-4 cycles ± rituximab + locoregional RT (30-40 Gy). In patients with adverse risk factors: CHOP 6-8 cycles ± rituximab ± locoregional RT (30-36 Gy)	CHOP21 × > 5 cycles + rituximab (CD20+). Abbreviated chemotherapy (+2 cycles after CR achievement recommended for low-intermediate risk patients	Patients without risk factors (increased β ₂ -microglobulin and/or B symptoms) and age <60 years: CHOP (or CHOP-like) × 3-4 + IFRT (36-40 Gy) Patients without risk factors and age >60 years: CHOP (or CHOP-like) × 3-4 ± IFRT Patients with risk factors: treat as stage III-IV	In patients without adverse risk factors, without mediastinal involvement and with less than two sites involved: abbreviated chemotherapy with an anthracycline-containing regimen plus locoregional RT. Locoregional RT only in elderly stage I patients without adverse risk factors and with contraindication to chemotherapy. Patients with more than 2 sites involved or adverse risk factors: treat as for stage III-IV disease
Stage I-II bulky		CHOP 6-8 cycles ± rituximab		Without risk factors: CHOP (or CHOP-like) × 6-8 ± IFRT (36-40 Gy) With risk factors: treat as stage III-IV	Treatment as for or stage III-IV.
Stage III-IV IPI 0-1	CHOP × 6-8 + rituximab	CHOP (preferred to other anthracycline-based regimens) 6-8 cycles ± rituximab (to be administered in all the pts >60 yrs).		CHOP (or CHOP-like) 6-8	CHOP, CHOP-like or third-generation chemotherapy + rituximab
Stage III-IV IPI >2		Enrollment in a clinical trial (i.e. SCT) is to be preferred or CHOP 6-8 cycles ± rituximab		CHOP (or CHOP-like) or CHOP+ rituximab or clinical trial	CHOP, CHOP-like or third-generation chemotherapy + rituximab
Consolidation RT		To bulky sites (30-40Gy) for stage III-IV disease	Considered for bulky sites	To bulky or residual masses	To bulky sites (30-36 Gy) for stage III-IV disease and CR or CRU

ly patients (Table 2).⁴⁸⁻⁵² Conversely, the strength of the recommendation for the use of rituximab differs among the guidelines, being quite low in the position paper by the Cancer Care Ontario Network.⁴⁸ This may be partially related to the different updating times of the guidelines. The present guidelines also agree with NCCN guidelines on the treatment of relapsed/refractory patients, while heterogeneous recommendations were provided by the ESMO, NCCN and the present guidelines on the duration of chemotherapy and radiotherapy dose (Table 2). The present recommendations on CNS prophylaxis are concordant with other author-based,⁵³ and evidence-based recommendations.⁴⁹

The present guidelines have some inevitable limits. They do not account for experimental therapies, such as thalidomide, and other monoclonal antibodies under investigation. We are also aware that the potential cost

implications of applying the recommendations have been only implicitly considered when formulating recommendations for high-cost drugs or procedures. However, economic evaluations have supported the cost-effectiveness of the two main recommendations of the present guidelines, namely HDT/auto SCT for relapsed patients,⁵⁴ and frontline chemoimmunotherapy.^{55,56} The present guidelines are expected to improve adherence to evidence-based practice to promote a rational use of novel technologies still under evaluation.

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