special article

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ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)

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To complete the existing treatment guidelines for all tumor types, ESMO organizes consensus conferences to better clarify open issues in each disease. In this setting, a consensus conference on the management of lymphoma was held on 18 June 2011 in Lugano, immediately after the end of the 11th International Conference on Malignant Lymphoma. The consensus conference convened ~45 experts from all around Europe and selected six lymphoma entities to be addressed; for each of them three to five open questions were to be discussed by the experts. For each question, a recommendation should be given by the panel, supported by the strength of the recommendation based on the level of evidence. This consensus report focuses on the three most common lymphoproliferative malignancies: diffuse large B-cell lymphoma, follicular lymphoma and chronic lymphocytic leukemia. A second report will concentrate on mantle cell lymphoma, marginal zone lymphoma and T-cell lymphomas.

Key words: chronic lymphocytic, consensus conference, diffuse large B-cell lymphoma, follicular lymphoma, leukemia, treatment

introduction

Level of evidence and grades of recommendation adapted from the Infectious Diseases Society of American–United States Public Health Service Grading System were used. They are summarized in Table 1.

diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most frequent lymphoma subtype, representing 30%–35% of all non-Hodgkin lymphomas. There has been a substantial improvement in understanding the biology and management of DLBCL over the last 10 years. Nevertheless, a significant number of issues remain controversial.

can the results of molecular biology, immunohistochemical subgrouping and clinical prognostic scores be used for management decisions?

The diagnosis of DLBCL should be established by an experienced hematopathologist with the help of immunohistochemistry, according to the WHO classification [1]. Gene expression profiling (GEP) can distinguish at least two major DLBCL subtypes [germinal center B cell-like (GCB)

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Table 1 LOE and GOR adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System†

I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials of large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Source: †Dykewicz CA. *Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001;33:139-144.*

and non-GCB/activated B cell-like (ABC)], which are genetically different diseases [2]. These subtypes present a different outcome when treated with chemotherapy alone or combined with rituximab [3]. GEP is still considered a research tool, because of the difficulties in applying it in routine practice: it requires fresh tissue specimens and it is expensive. Several immunohistochemistry-based algorithms were developed with the purpose of substituting GEP [4], but they showed limited reproducibility and until now no proven utility to help treatment decisions [5]. The Lunenburg consortium failed to demonstrate an improvement of the International Prognostic Index (IPI) by the inclusion of immunohistochemical markers [6], although some molecular markers such as c-myc expression or double hit lymphomas [7], found in a limited number of patients, are associated with a significantly worse prognosis.

The IPI for aggressive lymphomas was defined almost 20 years ago [8] and is still the most important clinical tool for assessing the prognosis of newly diagnosed DLBCL patients. Having been established before the advent of rituximab, the question of its validity was raised in the era of immunochemotherapy. Several attempts to improve the IPI were made: the British Columbia Cancer Agency proposed a revised IPI (R-IPI) for patients treated with immunochemotherapy [9], whereas US investigators presented a modified prognostic index for the elderly population (>70 years—E-IPI) [10]. The main limitation of these proposals is the relatively small number of patients and the lack of reproducibility. In the analysis of a large cohort of patients treated in prospective randomized trials with immunochemotherapy, the IPI retained its predictive value [11]. Therefore, the impact of different biomarkers as well as the GCB and non-GCB on prognostic estimation still has limited value in the rituximab era [5,6], and the IPI remains the most important prognostic tool.

recommendation 1.1

Gene expression profile examination and immunohistochemistry-based algorithms defining DLBCL subtypes are promising tools, but remain optional and are not ready to be applied to clinical decision making.

Level of evidence: IV
Grade of recommendation: C

recommendation 1.2

IPI remains the most powerful prognostic tool. Modified prognostic scores (R-IPI and E-IPI) have not been consistently validated and are not recommended for routine use.

Level of evidence: I
Strength of recommendation: A

is there a standard first-line treatment for young patients with DLBCL?

A number of studies demonstrate higher activity of new regimens compared with earlier ones, and many cooperative groups have developed their standards dividing patients by age and by risk factors.

For 'young, patients with a good risk profile' (low or low-intermediate IPI), R-CHOP is the standard treatment, and based on the results of the MINT trial, radiation therapy (RT) to the sites of primary bulky disease is recommended [12]. There is, however, a difference between IPI low-risk versus IPI low-intermediate risk or IPI low-risk with bulky disease; chemotherapy intensification might improve the outcome of the latter subgroups, based on the results of the randomized trial comparing R-ACVBP versus R-CHOP [13]; in this trial RT was omitted in both arms.

For 'young, IPI high-intermediate risk or high-risk patients', a consensus is difficult to reach. In this subset of patients, results of R-CHOP 21 or R-CHOP 14 are less satisfactory, with progression-free survival (PFS) <50% at 3 years. Attempts to improve the outcome have been and continue to be tested in several ways: increasing dose, number of drugs, dose intensity and/or including high-dose therapy (HDT) and autologous stem cell transplant (ASCT). The only direct comparison of R-CHOP 21 versus R-CHOP14 in a prospective randomized trial was conducted in the whole population of DLBCL and failed to demonstrate significant survival advantage of R-CHOP14 in the first analysis [14]. Moreover, in this trial R-CHOP 14 failed to show a better outcome in each DLBCL subset, including young patients with a poor risk profile. The trial was, however, not powered to compare different clinical subgroups. Dose-intensive regimens such as ACVBP and CHOEP14 have been used regularly in some countries for this group of patients [15, 16]. There is, however, no direct comparison of these regimens with or without rituximab (R) against CHOP 21 in this population. The consolidation by HDT and ASCT was tested in many randomized trials in the prerituximab era with contradictory results.

A meta-analysis of 13 randomized trials showed no overall survival (OS) benefit for HDT and ASCT [17]. In the rituximab era, four randomized trials comparing rituximab high-dose chemotherapy (R-HDCT) + ASCT versus R-chemotherapy have been presented (not yet published). Two trials show a PFS benefit for HDT with ASCT but no impact, at present, on survival [18, 19], whereas two trials failed to demonstrate an improvement for the HDT arm [20, 21]. HDT with ASCT in first line is therefore not recommended outside of clinical trials.

recommendation 2.1
The standard management of young patients with a good risk profile is R-CHOP21 × 6 for patients with low IPI risk without bulky disease.

Level of evidence: I
Strength of recommendation: A

recommendation 2.2
For young patients with low-intermediate IPI risk or low risk with bulk, either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP are recommended.

Level of evidence: II
Strength of recommendation: B

recommendation 2.3
There is no standard treatment for young patients with high-intermediate or high IPI risk. R-CHOP 21 may not be sufficient, and regimens more intensive than R-CHOP, such as R-CHOEP14, R-ACVBP, consolidation with HDT + ASCT or other intensive regimens may be offered to these patients, if possible in the setting of clinical trials.

Level of evidence: II
Strength of recommendation: B

how should elderly patients with DLBCL be managed?

The population of elderly patients (age >60 years) is not homogenous. The majority of trials are focused on patients aged 60–80 years. For them, a geriatric assessment is strongly recommended. R-CHOP 21 regimen (eight cycles) emerged as the preferred treatment choice in this population based on the results of the GELA study (LNH98-5), demonstrating that the addition of rituximab to CHOP21 improves PFS and OS [22]. The number of R-CHOP 21 cycles used in the most solid randomized trials was 8, but indirect evidence and some observations suggest that for patients in complete response (CR) after four cycles of R-CHOP 21, six cycles may be sufficient [23]. There have been attempts to use intensified treatment of this population, either R-CHOP 14 (six cycles of chemotherapy and eight cycles of rituximab demonstrated superior outcome over CHOP14 only or eight cycles of CHOP14 and eight cycles of rituximab) [24] or ACVBP which was demonstrated to be superior over standard CHOP for the population aged 61–69 years, in the prerituximab era [25]. Two trials have been presented (but not fully published) comparing R-CHOP14 versus R-CHOP21 in this patient population. The French trial was focused on elderly patients (60–80 years) and failed to demonstrate superiority for R-CHOP14 at a median observation time of 3 years [26]. The UK trial [14] was open for younger as well as for elderly patients, but the median age was 61 years. They did not demonstrate R-CHOP14 superiority over R-CHOP21 either. While the two regimens are equivalent in efficacy, R-CHOP14 has the advantage of being 3 months shorter, but the disadvantage of mandatory G-CSF support. For patients older than 80 years, the attenuated regimen R-miniCHOP was shown to be a reasonable option with good results [27]. The doxorubicin substitution with etoposide, or even its omission, can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or patients who are otherwise unfit.

recommendation 3.1
The standard management of elderly patients should be based on the general health status of patients (comorbidity).
For fit patients, R-CHOP21 × 8 or R-CHOP 14 × 6 + 2R

Level of evidence: I
Strength of recommendation: A

recommendation 3.2
For patients in CR after four cycles of R-CHOP 21, six cycles could be sufficient.

Level of evidence: II
Strength of recommendation: B

recommendation 3.3
For patients older than 80 years without significant cardiac dysfunction, R-miniCHOP21 × 6 can be recommended.

Level of evidence: III
Strength of recommendation: C

recommendation 3.4
For unfit patients with significant cardiac dysfunction, adriamycin substitution (e.g. etoposide) can be considered—R-C(X)OP21.

Level of evidence: IV
Strength of recommendation: C

management of relapsed DLBCL

For patients with relapsed/resistant DLBCL who are fit enough, a platinum-based salvage regimen followed by consolidation of the response with HDT and ASCT is considered the standard of care [28]. The question of which platinum-based regimen is superior was recently addressed, showing no differences between R-DHAP and R-ICE [29], although a recent subgroup analysis suggested that R-DHAP could achieve better results in GCB-like DLBCL [30]. Rituximab as part of the salvage therapy significantly improves the outcome of patients who were not previously treated with rituximab [31], while the impact of rituximab as part of the salvage therapy in patients previously treated with rituximab was not formally tested, although it is often used. According to some reports, the outcome of autotransplanted patients previously exposed to

rituximab is significantly worse compared with rituximab naive patients [29]. Other regimens showed efficacy in the relapsed setting, such as gemcitabine-based [32] oxaliplatin containing regimens [33]. Allogeneic stem cell transplantation (allo-SCT) should be considered in selected patients failing autologous stem cell transplantation or with very poor risk factors at relapse [34, 35]. Relapsed/refractory patients not eligible for HDT with ASCT may be treated in trials of novel agents or novel strategies.

recommendation 4.1
For young patients, rituximab and a platinum-based regimen should be used as salvage regimen.

Level of evidence: II
Strength of recommendation: B

recommendation 4.2
For chemosensitive patients, remission consolidation with HDT and ASCT is recommended.

Level of evidence: I
Strength of recommendation: A

recommendation 4.3
For patients ineligible for HDT with ASCT, a platinum- and/or gemcitabine-based regimen or the participation in a clinical trial can be proposed.

Level of evidence: III
Strength of recommendation: C

what is the role of whole-body positron emission tomography in the management of DLBCL?

Positron emission tomography (PET) is strongly recommended for pretreatment evaluation and for final response assessment [36, 37]. Two systematic reviews also confirmed the utility of PET as final examination [38, 39]. A negative PET scan after induction chemotherapy is associated with favorable outcome, although the positive predictive value (PPV) seems to be somewhat limited and histopathology confirmation should be considered. Positive interim PET scans are thought to be associated with inferior outcomes in DLBCL; however, contradictory results were recently reported failing to show a high PPV of interim PET [40]. Additionally, there is still only moderate reproducibility of the evaluation among nuclear medicine experts [41]. The use of interim PET results to guide treatment modification is not recommended due to the high proportion of false interim PET positive results [42]. Relapses during follow-up are detected in the majority of patients due to symptoms or routine clinical examination, but the impact of PET surveillance on relapse detection has been studied in some single-center series, showing an earlier detection of relapses by PET compared with clinical findings [43]. However, the benefit for the whole complete remission population seems to be very questionable, and cost is significantly higher compared with routine clinical or computed tomography surveillance.

recommendation 5.1
PET examination is recommended at initial staging.

Level of evidence: IV
Strength of recommendation: B

recommendation 5.2
PET examination is recommended for restaging at the end of systemic treatment.

Level of evidence: III
Strength of recommendation: A

recommendation 5.3
PET examination is not recommended for interim restaging in routine practice.

Level of evidence: III
Strength of recommendation: B

recommendation 5.4
Treatment modification based on interim PET restaging is not recommended.

Level of evidence: III
Strength of recommendation: B

recommendation 5.5
PET surveillance is not recommended as part of routine follow-up.

Level of evidence: III
Strength of recommendation: B

follicular lymphoma

Follicular lymphoma (FL) is the second most frequent non-Hodgkin lymphoma subtype, and it accounts for about 10%–20% of all lymphomas in western countries.

Treatment options for patients with naïve or recurrent FL are still controversial, ranging from a 'watch-and-wait' policy to hematopoietic stem cell transplantation.

what should be the initial therapy for patients with limited stage disease?

Patients with stage Ia and limited stage IIa diseases should be offered local radiotherapy (RT), because there is a chance of cure in this setting. Ten-year relapse-free survival rates of 43%–51% and 10-year OS rates ranging from 62%–79% are seen, as shown in Table 2. Relapse in these patients is generally outside the radiation field with a local PFS of ~80% at 5 years [44, 45].

Involved field RT should be given, delivering a dose of 24 Gy in 12 fractions [46]. Delivery of even lower doses of RT down to 4 Gy in two fractions are effective in FL in the palliative setting [47]. A large trial has recently been completed evaluating 4 Gy in the radical setting, but the results are not yet available.

Extended field and total nodal irradiation has been advocated by some, but in contrast to involved field, this is associated with greater toxicity, and no consistent gain has been identified from the use of larger radiation fields.

Table 2. Outcome of patients with stage I-II FL treated with local radiotherapy

Study	Number of patients	Freedom from relapse (10 years), %	Overall survival (10 years), %
Vaughan Hudson, BNLI, 1994 (1)	208	47	64
Pendlebury, Royal Marsden 1995 (2)	58	43	79
MacManus, Stanford 1996 (3)	177	44	64
Wilder MDAH 2001 (4)	80	41 (15 years)	43 (15 years)
Petersen PMH 2004 (5)	460	51	62
Eich Cologne 2009 (6)[a]	52	43	63[b]

[a]Includes follicular and centrocytic/centroblastic lymphoma.
[b]Survival data includes six patients with stage III disease treated with RT alone.
BNLI, British National Lymphoma Investigatoin; MDAH, M D Anderson Hospital; PMH, Princess Margaret Hospital.

Combined modality treatment has been proposed, but there is only one prospective study with mature results at a median follow-up of 10 years [48], in which 102 patients were treated with COP- or CHOP-Bleo followed by 30–40 Gy involved field RT. The results are similar to but not clearly superior to a series of RT alone, and no randomized trial of combined modality treatment has been undertaken. Moreover, in this setting, no data on the role of rituximab are available. This may be considered for patients with higher risk FLIPI or bulky disease, although there is no supporting evidence for superiority.

Results of observation alone after excision biopsy for stage I disease have also been reported. In a series of selected patients, 10-year OS ranges from 82.5%–86%. [49, 50]. However, an analysis from the SEER database [51] of 6568 patients treated in the United States between 1973 and 2004, having stage I or II and grade 1 or 2 FL demonstrates that in the 34% of patients who received RT, both OS and disease-specific survival was significantly better than those patients who did not receive RT with hazard ratios of 0.68 and 0.61, respectively. Observation should therefore only be considered in patients with a relatively short life expectancy due to comorbidity or other compelling reasons to avoid RT.

recommendation 1.1

Patients with stage Ia and limited stage IIa disease should be offered local RT delivering a dose of at least 24 Gy in 12 fractions.

Level of evidence: III
Strength of recommendation: B

when should treatment be initiated in patients with advanced stage FL?

Several studies before the rituximab era have demonstrated that, in patients with advanced stage 'asymptomatic' FL, there is no advantage in terms of OS for immediate treatment compared with a watchful waiting approach [52–54].

The criteria used by large cooperative groups to determine when a watch-and-wait approach was suitable are listed in Table 3. The 'Groupe d'Etude des Lymphomes Folliculaires' criteria are more restrictive and have served as trial entry criteria. Therapy may still be deferred in patients with features of high tumor burden (i.e. >3 lymph nodes measuring >3 cm or a single lymph node >7 cm) and no other features mandating therapy, but these patients are likely to require treatment sooner than low tumor burden patients and they should therefore be monitored closely.

The advantage of observation is that it can safely defer the initiation of systemic therapy by a median of 2–3 years so that patients are spared for some time the toxic effects of chemotherapy. In one study, in patients over the age of 70, 40% had not received chemotherapy at 10 years after diagnosis [52]. Patients who undergo observation do not have an increased risk of high-grade transformation [53, 55, 56] compared with those who commence therapy immediately.

However, these studies were all carried out before the demonstration of improved OS by the addition of rituximab to chemotherapy in patients in need of treatment. Hence, the benefit of delaying the administration of immunochemotherapy is unknown.

recommendation 2.1

Observation alone is an appropriate strategy in patients with asymptomatic, advanced stage FL in an attempt to delay the side effects of chemotherapy.

Treatment should be initiated only upon the occurrence of symptoms or signs due to lymphoma, including:

1) B symptoms
2) Symptomatic or life-endangering organ involvement
3) Significant ascites or pleural effusion related to lymphoma
4) Rapid lymphoma progression
5) Hematopoietic impairment due to significant marrow infiltration by lymphoma

The presence of bulky disease (defined as more than three nodal sites with a diameter of >3 cm or the largest nodal or extranodal mass measuring >7 cm) or an elevated LDH or β2-microglobulin may prompt treatment even in the absence of the features listed above. Observation may also be chosen for this group of patients but they should be monitored closely as they are likely to progress rapidly.

Level of evidence: II
Strength of recommendation: B

choice of therapy in newly diagnosed advanced FL needing treatment

In the majority of patients with symptomatic advanced stage disease, systemic immunochemotherapy is usually prescribed. Four prospective studies in the first-line setting demonstrated an improved overall response, PFS and OS when rituximab was added to chemotherapy [57–60] (Table 4).

Moreover, a randomized trial show that bendamustine and rituximab as first-line treatment is at least as good in respect of PFS and CR rate when compared with CHOP plus rituximab [61].

Table 3. Available criteria for defining active disease requiring systemic therapy in patients with Follicular lymphoma

GELF criteria	SIE/SIES/GITMO criteria (Adapted by Federico et al. 2011)	BNLI criteria
• High tumor burden defined by at least one of the following Involvement of three distinct nodal sites, each with a diameter of 3 cm Any nodal or extranodal (except spleen) tumor mass with a diameter of 7 cm Symptomatic splenomegaly (enlarged spleen) Cytopenias (leukocytes <1.0 × 10/l and or platelets <100 × 10/l) Leukemia (>5.0 × 10/l malignant cells) Pleural effusions or peritoneal ascites • B symptoms • Elevated LDH (≥ UNV) or β2-microglobulin (≥3 g/dl) • ECOG PS (≥1)	• Involvement of three nodal sites, each with a diameter of at least 3 cm • Any nodal or extranodal mass with diameter >7 cm • Splenic involvement or splenomegaly • Leukemia • Pleural effusions or peritoneal ascites • Cytopenias due to lymphoma • Extranodal disease • Compressive syndrome due to lymphoma • B symptoms • ESR >20 mm/h • Elevated LDH (≥UNV)	• Progressive disease within 3 months form diagnosis • Involvement of vital organs • Kidney or liver involvement • Bone lesions • B symptoms or pruritus • Cytopenias (hemoglobin <100 g/l or leukocytes <3.0 × 10^9/l or platelets <100 × 10^9/l

ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; UNV, upper normal value; GELF, Groupe d'Etude des Lymphomes Folliculaires; ECOG, Eastern Cooperative Oncology Group; SIE, Italian Society of Hematology; SIES, Italian Society of Experimental Hematology; GITMO, Gruppo Italiano Trapianto Midollo Osseo; BNLI, British National Lymphoma Investigation.

Table 4. Combined immunochemotherapy in follicular lymphoma (first line)

Regimen	*N* patients	Median follow-up (months)	R-Chemo versus Chemo		
			CR-CRu (%)	ORR (%)	Efficacy
CVP ± R	321	30	41 versus 10	81 versus 57	TTP: 32 versus 15 mo
CHOP ± R	428	24	20 versus 17	96 versus 90	2-year PFS: 84% versus 63%
MCP ± R	358	30	49 versus 25	92 versus 75	2-year EFS: 83% versus 43%
CHVP ± R	358	60	63 versus 34	94 versus 85	5-year EFS: 53% versus 37%

Recently, a prospective randomized trial comparing R-CVP versus R-CHOP versus R-FM (fludarabine and mitoxantrone) documented a better failure free survival in favor of R-CHOP and R-FM over R-CVP, but at 2-year median follow-up, the survival was the same in the three arms [62]. However, the rate of secondary neoplasias was significantly increased in the R-FM arm. Finally, initial therapy with R-CHOP was associated with an improved OS in comparison with R-FCM in patients enrolled in the PRIMA study and maintained with R for 2 years [63], but this comparison was not randomized.

In conclusion, if complete remission and long-lasting disease control is the desired objective, rituximab in combination with chemotherapy (R-CHOP, R-CHVP, R-CVP, R-bendamustine or R-chlorambucil) is recommended.

In cases when chemotherapy is not desired, treatment with single-agent rituximab followed by rituximab maintenance can be given, with ~70% chance of response and a median duration of response of 2–4 years [64].

A systematic review and meta-analysis of randomized trials documented the efficacy of rituximab maintenance for the treatment of patients with FL [65]. More recently, the PRIMA study demonstrated that rituximab maintenance for 2 years improves PFS (75% versus 58% after 3 years, $P < 0.0001$) with an excellent safety profile, and mild and infrequent side-effects [63]. Finally, a prolongation of PFS can be achieved with radioimmunotherapy consolidation after chemotherapy, although its benefit following rituximab combinations has not been established [66].

recommendation 3.1

Rituximab with chemotherapy (such as CVP, CHOP, bendamustine, chlorambucil or others) is considered the standard treatment of patients with FL in need of treatment.

Level of evidence: I
Strength of recommendation: A

recommendation 3.2

Single-agent rituximab is an option when the side-effects of chemotherapy are to be avoided.

Level of evidence: II
Strength of recommendation: B

recommendation 3.3

Maintenance with rituximab significantly prolongs remission with minimal side-effects and should generally be offered to all patients.

Level of evidence: I
Strength of recommendation: A

what are the indications for stem cell transplantation in FL?

Three randomized trials comparing HDT with ASCT versus conventional chemotherapy to consolidate first remission were published before the rituximab era [67–69]. There was an advantage in terms of PFS or event-free survival in two studies, but this was not translated into any difference in OS. In two of the studies, there was a significant increase in the rate of secondary malignancies in the HDT arm, which might have accounted for the lack of difference in OS. A fourth study in the rituximab era confirmed the advantage in PFS without OS improvement [70].

The only randomized study comparing HDT with conventional chemotherapy in patients with relapsed FL demonstrated an advantage in both PFS and OS for HDT over chemotherapy [71], but this study was prematurely closed due to poor recruitment, and some reservations regarding its results have been expressed. Three retrospective studies of HDT with ASCT in relapsed FL with a long follow-up (median: 8–12 years) show a plateau in the PFS curve [72], pointing to the possibility of a cure for a subset of patients with FL receiving HDT at relapse. Of note, all of these studies were carried out in the prerituximab era. More recently, a randomized study (only presented in abstract form) [73] has shown a significantly prolonged PFS in patients receiving rituximab maintenance following HDT for relapsed FL, and three *ad hoc* analyses of prospective studies have shown a positive impact on outcome for both rituximab and autologous transplant at relapse [74–76].

A considerable number of articles have been published on the outcome of FL (or 'indolent' lymphoma) following reduced intensity conditioning (RIC) transplant. These studies are highly heterogeneous in terms of the population included (i.e. the percentage of patients having a RIC transplant after HDT with ASCT) and the characteristics of the transplant (i.e. proportion of unrelated donors included).

No randomized studies have compared outcomes following RIC allogeneic transplant and HDT with ASCT but retrospective studies have shown no difference in OS, the lower relapse risk of RIC transplant being outweighed by higher nonrelapse mortality [77].

recommendation 4.1

HDT with autologous stem cell rescue is not recommended to consolidate first remission outside of clinical trials.

Level of evidence: I
Strength of recommendation: A

recommendation 4.2

HDT with autologous stem cell rescue is recommended at first relapse in patients with a poor prognosis (i.e. those with a short duration of first response).

Level of evidence: III
Strength of recommendation: B

recommendation 4.3

Both HDT and RIC allogeneic transplants are options to be considered in patients in second or subsequent relapse.

Level of evidence: IV
Strength of recommendation: C

chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults. Important progress has been achieved in understanding the biology of the disease and more effective therapies are available. Clinical practice guidelines for diagnosis, treatment and follow-up of CLL patients have been recently updated and published, including by ESMO in 2011 [78, 79].

how should we deal with autoimmunity in patients with CLL?

The CLL dysregulated immune system favors the development of autoimmune disorders. Autoimmune hemolytic anemia (AIHA) and, to a lesser extent, autoimmune thrombocytopenia (ITP), are relatively frequent in CLL (5%–7%), while pure red cell aplasia and autoimmune granulocytopenia are very uncommon. Despite regular case reports, there is no proof of a link between non-hemic autoimmune disorders and CLL, the only exception being paraneoplastic pemphigus [80–84].

Autoimmune disorders are particularly common in advanced phases of the disease. The concept that autoimmune cytopenia may precede CLL should be revisited in the light of recent data showing that autoimmune cytopenia may be observed in monoclonal B-cell lymphocytosis, a condition that can only be detected by using sensitive flow cytometric techniques [81, 82].

The causes and physiopathology of autoimmune cytopenias in CLL are only partially understood. More than 90% of autoimmune disorders in CLL are caused by nonmalignant B lymphocytes that produce polyclonal high-affinity immunoglobulin G (IgG) via a T-cell-mediated mechanism. IgG-opsonized cells are subsequently destroyed via antibody-dependent cellular cytotoxicity. The implication is that CLL cells exert a yet undefined influence on nonmalignant lymphocytes, both T and B cells, that results in the development of autoimmunity. The question of which normal bystander cells are involved in this process (and how) underlines the importance of further analysis of microenvironment bystander cells. CLL tumor cells can act as antigen-presenting cells, inducing the formation of both autoreactive T-helper cells (through the production of B-cell-activating factor and a proliferation-inducing ligand) as well as nonfunctional T-regulatory cells (via CD27-CD70 interaction) [81, 85].

It has been proposed that cytopenias complicating CLL may be classified into two groups: 'simple autoimmunity' (stable CLL disease) and 'complex autoimmunity' (concomitant CLL progression) [83]. Autoimmune cytopenia is not necessarily associated with poor prognosis. On the contrary, patients with anemia or thrombocytopenia due to immune mechanisms

have a better outcome than those in whom these features are due to bone marrow infiltration by the disease [83, 84]. Moreover, fears about the risk of autoimmune hemolysis following single-agent fludarabine are no longer appropriate in the age of chemoimmunotherapy regimens. In fact, the incidence of autoimmune cytopenia in patients treated with chemoimmunotherapy is lower than in those receiving chemotherapy only (reviewed in 81). The first treatment option for patients with autoimmune cytopenia with warm antibodies is corticosteroids. Autoimmune cytopenia not responding to conventional autoimmune therapy is an indication for CLL treatment [78, 79]. In selected patients not responding to steroids, monoclonal antibodies (mAbs) such as rituximab could be used before splenectomy, which is still a preferable option in most patients with refractory or relapsing autoimmune hemolysis with warm antibodies, whereas rituximab is mostly a better treatment option in patients with cold antibodies. Patients with ITP should be initially treated with corticosteroids; rituximab, immunosuppressors and splenectomy being treatment options in refractory cases. In a few reports, thrombopoietin analogs have been shown to be effective in ITP-related CLL not responding to corticosteroids (reviewed in 82). As with AIHA, refractory ITP is an indication for starting CLL therapy [78, 79].

recommendation 1.1
Autoimmune disorders should not be considered a marker of CLL progression.

Level of evidence: III
Strength of recommendation: B

recommendation 1.2
The first treatment option for patients with autoimmune cytopenia with warm antibodies is corticosteroids.

Level of evidence: III
Strength of recommendation: B

recommendation 1.3
Autoimmune cytopenias not responding to conventional autoimmune-oriented therapy are indications for CLL treatment.

Level of evidence: III
Strength of recommendation: B

can a risk-adapted therapy be based on biological risk factors?

Some patients with CLL have a normal lifespan and never require therapy while others have a rapidly fatal disease despite therapy [78, 79, 86]. This heterogeneity is in part accounted for not only by clinical parameters such as the tumor burden, which is best reflected by Rai or Binet clinical stages, but also by the biological diversity of the disease. Based on the assessment of B-cell receptor structure and function, different CLL subtypes (i.e. immunoglobulin heavy variable unmutated or mutated) with distinct biological and clinical characteristics have been identified [87, 88]. Recurrent genomic aberrations such as del(11q) and del(17p) and mutations of *TP53* also help in defining biological and clinical subgroups [89, 90, 91]. In addition, serum (e.g. β2-microglobulin) and cellular markers (e.g. CD38, ZAP70) correlate with clinical outcome (reviewed in [86]).

Currently, the only biological parameters useful to guide treatment are deletion del (11q), del(17p) and *TP53* mutation [79]. Patients with del(11q) usually have short PFS with traditional alkylator-based chemotherapy, which however can be overcome by chemoimmunotherapy, such as fludarabine, cyclophosphamide and rituximab (FCR) [92–94]. On the other hand, remission rates, PFS and OS of patients with del(17p) or *TP53* mutation are poor [91]. This applies to chemotherapy alone, chemoimmunotherapy and immunomodulators.

There are no clinical trials comparing alemtuzumab or allo-SCT against standard first-line treatment (i.e. FCR), and therefore, no firm recommendation can be given as to the best treatment approach for these patients. Based on single-arm phase II studies, it is considered that alemtuzumab, particularly when combined with corticosteroids, can be effective [95]. Allo-SCT is however the only treatment actually active in that setting [96] (see also the section on allo-SCT, below). Based on these data, alemtuzumab and allo-SCT are considered valid therapies for CLL with del(17p)/*TP53* mutation. It is highly recommended that patients with del(17p) or *TP53* mutation are offered allo-SCT early, before resistance to therapy or disease transformation occurs.

recommendation 2.1
Even though many biological markers have been associated with prognosis, none of them have been clearly shown to be sufficiently predictive to be used for treatment decisions, except for del(11q), del (17p) and TP53 mutation.

Level of evidence: I
Strength of recommendation: A

recommendation 2.2
In patients with del(11q), chemoimmunotherapy with FCR has been shown to result in a longer PFS than other regimens (e.g. fludarabine and cyclophosphamide).

Level of evidence: I
Strength of recommendation: A

recommendation 2.3
For patients with del(17p)/TP53 mutation, alemtuzumab along with corticosteroids is an alternative to FCR for remission induction, and allo-SCT should be considered for consolidation in eligible patients once they achieve response.

Level of evidence: III
Strength of recommendation: B

how should CLL in the elderly be managed?

Elderly patients are under-represented in clinical trials. As management of patients with CLL should not be modulated by 'chronological' but 'biological' age, it is important to identify factors which recognize frail or vulnerable patients ('slow-go',

'no-go') patients in contrast to fit patients ('go-go') by means of comorbidity and functional activity (fitness) scores and include these patients in specific fitness-based trials [97].

The FCR regimen changed the prognosis of younger fit CLL patients, but its role in elderly patients needs further clarification. In the FCR phase II trials from MD Anderson, the subgroup of elderly patients showed a significantly lower CR rate, with longstanding cytopenia and infections being the main cause for premature treatment discontinuation [92, 93]. In an international randomized trial, elderly fit ('go-go') patients had no significant difference in toxicity compared with younger patients, with response rates and PFS being similar [94].

Although intensive treatments can be given to physically fit elderly patients, treatment–toxicity is of concern. An alternative chemoimmunotherapy regimen combining rituximab with bendamustine (BR) has been suggested to be less toxic than FCR [98]. Currently, the German CLL Study Group 10 (GCLLSG10) trial is comparing both regimens (i.e. FCR and BR) in patients without comorbidities. Studies have also investigated reduction of treatment-related toxicity, lower doses of chemotherapeutic agents (e.g. fludarabine, pentostatin and cyclophosphamide) with or without rituximab with some encouraging but not yet definitive results [99–102].
Chlorambucil, the first available treatment of CLL, is still being used in the elderly, although fludarabine, bendamustine and purine analogs (i.e. fludarabine, pentostatine and cladribine) and cyclophosphamide induce CR more often than chlorambucil and also yield a longer time to treatment failure. In a randomized trial from the GCLLSG, specifically designed for elderly patients, no advantage of fludarabine over chlorambucil was found [103]. In the British CLL4 trial, including 30% of patients older than 70 years of age, three regimens were compared: (i) fludarabine plus cyclophosphamide; (ii) fludarabine and (iii) chlorambucil. Fludarabine and cyclophosphamide (a regimen that can be orally administered) resulted in higher CR rate and a significantly improved PFS in all age groups, but there were no differences in OS [104]. A randomized trial from Cancer and Leukemia Group B comparing chorambucil versus fludarabine showed a higher CR and longer PFS with fludarabine but, again, no differences in survival were observed when results were published, most likely due to the treatment cross-over effect [105]. In a randomized multicenter study comparing chlorambucil and bendamustine in previously untreated patients, bendamustine resulted in higher OR and CR and also a longer PFS but no survival benefit, with this being true in all age groups [106].

Several phase II trials have tested the addition of rituximab to chlorambucil in elderly patients. In one trial, an increase in CR rate and PFS was seen compared with historical controls; toxicity seemed to be higher in the elderly [107]. A phase II trial including only elderly patients and evaluating chlorambucil plus rituximab followed by maintenance with rituximab or no further therapy has shown positive interim results [108].

In a randomized phase III trial comparing chlorambucil to alemtuzumab, the overall response rate (ORR) and PFS were significantly higher with alemtuzumab. In the group of patients ≥65 years (35% of all patients included in the study) no differences in ORR and PFS were seen between the treatment arms. However, alemtuzumab was more effective in patients with del(17p) and del(11q) than chlorambucil, independently of age [109]. Thus, alemtuzumab can also be considered a treatment option in the elderly.

Recently, ofatumomab, a new anti-CD20 mAb, has been approved for treatment of CLL patients refractory to both fludarabine and alemtuzumab, due to a high response rate (although not complete) observed in all age groups in a phase II trial [110].

recommendation 3.1

Elderly CLL patients with good physical status and low comorbidity should be treated with chemoimmunotherapy.

Level of evidence: II
Strength of recommendation: B

recommendation 3.2

For elderly CLL patients with comorbidity.

Chlorambucil as single agent remains a reasonable treatment option.
Level of evidence: II
Strength of recommendation: B

Regimens consisting of purine analogs and cyclophosphamide at low doses with or without rituximab can be useful in patients with impaired renal function or comorbidity.
Level of evidence: III
Strength of recommendation: B

Bendamustine is another treatment option in patients with reduced renal function.
Level of evidence: II
Strength of recommendation: B

Alemtuzumab is recommended in elderly patients with CLL and del(17p)or TP53 mutation.

Level of evidence: II
Strength of recommendation: B

what is the role of allo-SCT in CLL?

In 2006, the European Group for Blood and Marrow Transplantation (EBMT) worked out a consensus on indications for allo-SCT in CLL, indicating that allo-SCT is a reasonable treatment option for eligible patients with previously treated, poor-risk CLL [111]. Criteria for 'poor-risk CLL' according to this 'EBMT Transplant Consensus' are any of the following: (i) nonresponse or early relapse (within 12 months) after purine analogs treatment; (ii) relapse within 24 months after having achieved a response with purine-analog-based combination therapy or autologous transplantation; or (iii) patients with *p53* abnormalities requiring treatment.

The emergence of new treatment options and prognostic markers during recent years will make it necessary to review these recommendations. However, for patients with high-risk disease because of del(17p), *TP53* mutations or purine-analog refractoriness, FCR does not seem to improve their dismal natural course. Similarly, fludarabine, cyclophosphamide and

Table 5. Results of T-replete alloSCT in 17p- and fludarabine-refractory CLL

	17p-refractory CLL				Fludarabine-refractory CLL			
Conditioning regimen	*n*	Relapse	PFS	Ref.	*n*	Relapse	PFS	Ref.
Fludarabine/TBI 2 Gy	7	2 of 7 (29%)	57% (3 years)	[123]	82[a]	38% (5 years)	39% (5 years)	[123]
Fludarabine/cyclophosphamide	13	41% (4 years)	45% (4 years)[b]	[96]	42	36% (4 years)	41% (4 years)	[96]
Fludarabine/cyclophosphamide/rituximab					86[c]	n.a.	36% (5 years)[d]	[124]
Fludarabine/cyclophosphamide/thiotepa	6	1 of 6 (17%)	33% (2 years)	[126]				
Miscellaneous	44	34% (5 years)	37% (3 years)	[91]				
Miscellaneous	6	1 of 6 (17%)	33% (3 years)	[125]				

[a]88% of these 82 patients were fludarabine refractory.
[b]Six of seven patients with sustained CR were MRD-negative at latest follow-up.
[c]83% of these 86 patients were fludarabine refractory.
[d]'Current' progression-free survival.
PFS, progression-free survival; TBI, total body irradiation.

ofatumumab [112], alemtuzumab either alone or in combination with corticosteroids and/or fludarabine [113], flavopiridol [114] and lenalidomide [115] do not provide sustained disease control. Importantly, retrospective analyses from prospective trials have provided sound evidence that patients with *TP53* mutation have an equally bad natural course as those with del(17p) [91, 116, 117]. The European Research Initiative on CLL (ERIC) has recently published recommendations regarding the methodology to study *TP53* mutations [118].

For patients whose disease is refractory to purine analogs, the published phase-II evidence indicates that allo-SCT can overcome the poor prognostic impact of purine-analog refractoriness, particularly if the patient can be entered into a state of sensitive disease before transplant (Table 5). Subset data from prospective phase-II studies as well as a larger registry analysis strongly suggest that long-term disease control can be achieved in 30%–45% of patients with del(17p) after allo-SCT (Table 5). A *post hoc* analysis of the GCLLSG CLL3X trial indicates that this is also true for patients with *TP53* mutation in the absence of del(17p) [119] (Tables 6–8).

For patients at high risk because of early progression after chemoimmunotherapy (i.e. <24–36 months), there are no detailed studies concerning the effect of individual salvage regimens. However, the overall outlook of these patients is poor. In a retrospective analysis of patients of the German CLL8 trial, the OS after start of salvage treatment of patients whose disease progressed within the second year after the end of treatment was about 2 years, comparable to that of truly refractory patients [120]. Similarly, a time to FCR failure <36 months was a significantly adverse factor in a study from the MD Anderson group, along with treatment with more than three lines of therapy and del(17p) [121, 122].

There is no structured data available on the specific effect of allo-SCT in patients experiencing early (<24–36 months) relapse. However, as the prognosis of these patients is equally as bad for those with fludarabine-refractory disease, and there is no fundamental biological difference between them, allo-SCT should be at least as effective in these patients as in those with true purine-analog refractoriness.

recommendation 4.1

Allo-SCT is the only treatment with the potential of providing long-term disease control for poor-risk CLL defined as del (17p), mutations TP53, purine-analog refractoriness and early relapse (<24–36 months) after chemoimmunotherapy.

Eligible patients should be discussed with a transplant center as soon as they fulfill poor-risk criteria to avoid development of further treatment resistance or disease transformation.

Level of evidence: III
Strength of recommendation: B

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Table 6. Recommended treatment strategies in diffuse large B cell lymphoma

Young < 61 years		
IPI low risk no bulk	IPI low risk with bulk or IPI low-intermediate risk	IPI intermediate-high risk or IPI high risk
R-CHOP21 × 6	R-CHOP21 × 6 + IF-RT on bulk or R-ACVBP	R-CHOP21 × 8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens: R-CHOEP14 × 8 or R-ACVBP or R-dose-dense (R-CHOP14 like) plus R-HDCT with ASCT
Consider CNS prophylaxis in patients at risk for CNS progression, i.e. involvement of: paranasal sinus, testicular, epidural, bone marrow (large cell) or ≥2 extranodal sites and elevated LDH level		
Elderly > 60 years		
FIT	>80 years without cardiac dysfunction	UNFIT or FRAIL or >60 years with cardiac dysfunction
R-CHOP21 × 8 or R-CHOP14 × 6 with 8 R	attenuated regimens: R-miniCHOP21 × 6	Doxorubicine substitution with etoposide or liposomal doxorubicine or others: R-C(X)OP21 × 6 or palliative care
Consider CNS prophylaxis in patients at risk		
First relapse/progression		
Eligible to transplant	Not eligible to transplant	
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE) as salvage treatment For chemosensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor risk factors at relapse	Platinum and/or gemcitabine based regimens Clinical trials with novel drugs	

IPI, international prognostic index; R-HDCT, rituximab-high dose chemotherapy; CNS, central nervous system; LDH, lactate dehydrogenase; ASCT, autologous stem cell transplantation.

Table 7. Recommended treatment strategies in follicular lymphoma

Stage I/II	Stage III/IV with low tumor burden	Stage III/IV with high tumor burden
Radiotherapy (involved field) 24–36 Gy in selected cases: watchful waiting	Watch and wait in symptomatic cases: consider Rituximab monotherapy or immunochemotherapy	Immunochemotherapy (e.g. R-CHOP, R-CVP, BR) In selected cases: Rituximab monotherapy CR/PR: consider Rituximab maintenance (up to 2 years) radioimmunotherapy
1. relapse/progression		dependent on prior regimen and remission duration:
• Immunochemotherapy • In selected cases: palliative radiation (e.g. 2 × 2 Gray)	- Immunochemotherapy (e.g. R-CHOP, R-CVP, BR, R-FC) - discuss HDT with ASCT • in selected cases: Rituximab monotherapy	• Immunochemotherapy: e.g. BR, R-CHOP, R-CVP, R-FC • discuss HDT with ASCT (if < 65 years) • Rituximab-maintenance (up to 2 years) • Alternatively radioimmunotherapy

CR, complete response; PR, partial response; HDT, high dose therapy; ASCT, autologous stem cell transplantation.

Table 8. CLL: front-line therapy based on genetic features, age and comorbidity

Genetics	Age (years)	Comorbidity	Standard treatment	Experimental treatment
TP53 deletion/mutation	<70	Fit patients	Alemtuzumab–Corticosteroids	CDK inhibitors
			FCR	PI3K inhibitors
			Allogeneic SCT[a]	BTK inhibitors
				Bcl-2 inhibitors
		Unfit patients[b]	Alemtuzumab–Corticosteroids	CDK inhibitors
				PI3K inhibitors
				BTK inhibitors
				Bcl-2 inhibitors
No *TP53* deletion/mutation	<70	Fit patients	FCR	BR
		Unfit patients[b]	Chlorambucil	BR
			or	Low-dose FCR
			Bendamustine	Lenalidomide
				Chlorambucil–rituximab
				CDK inhibitors
				PI3K inhibitors
				BTK inhibitors
				Bcl-2 inhibitors

Most patients older than 65 years are considered as 'unfit' for intensive treatment.

[a]Upper age limit for allogeneic stem cell transplantation in most transplant centers is 60–70 years.

[b]Based on chronic illnesses evaluation scores; creatinine clearance <60 ml/min.

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disclosure

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