SIE, SIES, GITMO revised guidelines for the management of follicular lymphoma

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By using the GRADE system, we updated the guidelines for management of follicular cell lymphoma issued in 2006 from SIE, SIES, and GITMO group. We confirmed our recommendation to frontline chemoimmunotherapy in patients with Stage III–IV disease and/or high tumor burden. Maintenance rituximab was also recommended in responding patients. In patients relapsing after an interval longer than 12 months from frontline therapy, we recommended chemoimmunotherapy with non cross-resistant regimens followed by rituximab maintenance. High dose chemotherapy followed by hematopoietic stem cell transplant was recommended for young fit patients who achieve a response after salvage chemoimmunotherapy. Am. J. Hematol. 88:185–192, 2013.

Introduction

Follicular cell lymphoma (FL) is a frequent disorder for which several treatment options have been recently proposed. In order to promote widespread adoption of appropriate clinical practice, the Italian Society of Hematology (SIE), and the affiliate societies SIES (Società Italiana di Ematologia Sperimentale) and GITMO (Gruppo Italiano Trapianto Midollo Osseo) established regular updating of published guidelines. Previous guidelines addressed indolent non-Hodgkin's lymphomas (NHL) [1], but more recently, specific treatment options were devoted to FL; therefore, current guidelines are specifically directed to the management of FL. In the 2008 WHO classification, grade 3b FL were separated and are universally treated as diffuse large B-cell lymphoma (DLBCL) [2]. Therefore, the present guidelines targeted grade 1-2-3a FL. We used the GRADE (grades of recommendation, assessment, development, and evaluation) system [3], which is based on a sequential assessment of the quality of evidence followed by an analysis of the benefit-risk balance and subsequent judgment about the strength of recommendations.

Methods

Guidelines development process. The Advisory Council (AC), composed of three members with expertise in clinical epidemiology, hematology, and critical appraisal, oversaw the process. An Expert Panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program [4]. During a first meeting, the EP decided which clinical issues needed an update and the AC checked which clinical queries might be addressed by a critical appraisal of evidence [3].

Producing and grading evidence-based recommendations. The AC selected the clinical questions that needed to be addressed by a critical appraisal of evidence. The EP chose the critical outcomes for each clinical query. Literature search was performed in July 2011 and limited to English-language publications edited after 2005. The search included proceedings 2009 through 2010 of the American Society of Hematology, the European Hematology Association, and the 11-ICML (11th International Conference on Malignant Lymphoma). According to GRADE methodology [3], the AC prepared "evidence tables" and "quality of evidence tables" (available by the corresponding author on request) for each critical appraisal. The EP received the critical appraisals and was asked to draft recommendations based on the benefit to risk profile of each compared intervention. Definite agreement of the recommendations and of their strength (weak or strong) was made through subsequent face-to-face meetings.

Producing consensus-based recommendations. The consensus methodology was applied by the EP for all the issues worth to be updated but not addressable by a critical appraisal. During three consecutive consensus conferences, the issues were analyzed and discussed according to the nominal group technique, as previously described [5].

Results

Issue 1: Staging (consensus-based recommendations)

FL is a (18)F-FDG avid disease, since more than 90% of patients with FL show a PET positive disease and sensitivity of staging PET is usually higher than 95% [6–9]. Published literature includes 10 retrospective analyses [9–18] and 1 prospective one [19]: pooled analysis of 356 patients revealed that 24% were upstaged from Stage I–II to Stage III–IV. Baseline PET also showed to have a high prognostic value, irrespective of FLIPI [10,11,17,19]. No study reported the clinical outcomes in patients in which the therapy was adjusted according to a PET-staged disease. The assessment of bone marrow involvement by PET is not reliable due to low sensitivity [8,9,20]. Globally, the analyzed studies showed a moderate quality.

The predictive role of pretreatment BCL2/IgH levels in bone marrow and peripheral blood is still controversial. In a seminal study, Rambaldi et al. [21] showed that the pres-

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Conflict of interest: Nothing to report

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Contract grant sponsors: SIE, SIES, GITMO Societies, Mundipharma, Janssen Cilag, Celgene, Roche (Italy).

Received for publication 8 June 2012; Revised 15 November 2012; Accepted 19 November 2012

Am. J. Hematol. 88:185–192, 2013.

Published online 10 December 2012 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.23372

ence of less than 1/1,000 BCL2/IgH (+) cells in the bone marrow was the best predictor of complete response after first-line treatment and levels less than 1/100 a good predictor of five-year event-free survival (EFS). However, this result has not been validated, and in 238 patients with refractory-relapsed FL enrolled into the EORTC 20981 phase III trial, a BCL2 positive bone marrow was associated with a worse progression-free survival (PFS) but the BCL2/IgH levels were not correlated with the rates of post-induction response [22]. However, recognizing that FLIPI was validated in the prerituximab era [23], a FLIPI 2 score including age, serum beta2 microglobulin, hemoglobin concentration, bone marrow involvement and tumor burden correlating with the longest diameter of the largest involved lymph node was recently proposed [24]. Both indexes have not been validated in prospective trials; therefore, they cannot be used to inform treatment decision in clinical trials.

Recommendations Appropriate staging is a fundamental step in the initial approach to patients with FL. Initial work-up should include a CT scan of the neck, thorax, abdomen and pelvis, and a bone marrow biopsy. FL is a FDG avid disease and PET allows the identification of a higher number of nodal and extranodal areas compared with CT scan. PET scan should be included in staging of patients with limited-stage disease at CT scan and possibly candidates to radiotherapy only. The panel agreed that PET upstaged patients should receive a therapy according to the new stage, even though there is no evidence that this choice is able to improve the outcome of the disease.

Pretreatment PET is also advisable to allow an optimal assessment of response for those patients needing chemotherapy in which an early stage disease (i.e., Stage II) and therapy fitness make the probability of CR high. Staging should be assigned according to the Ann Arbor system. Bone marrow biopsy histology should be performed with monolateral upper posterior iliac spine biopsy of at least 20 mm length and should include appropriate immunohistochemistry for the lymphomatous tissue. A complete blood count and routine blood chemistry including LDH, beta2microglobulin and uric acid are required. Like for all patients' candidate to receive cytotoxic and/or immunomodulatory drugs, screening for main infectious diseases, including HIV and hepatitis B and C, is recommended. Bone marrow and peripheral blood tests with polymerase chain reaction for t(14;18) chromosomal translocation and/or for immunoglobulin gene rearrangement (Ig CDR3) is not recommended for routine assessment and outside clinical trials. A follicular lymphoma international prognostic index (FLIPI) ($>$4 nodal sites, elevated LDH, age $>$60 years, Stage III–IV, hemoglobin $<$12 g/dl) should be determined in all the patients.

Issue 2: When to start treatment (consensus-based recommendations)

Based to the lack of overall survival (OS) improvement after treatment of asymptomatic advanced-stage patients [25], and according to the previous SIE guideline edition [1] and to GELF data [26], the panel agreed on the following recommendations.

Recommendations Treatment can be started in patients with Stage II–IV disease in case of one of the following features occurs: systemic symptoms, high tumor burden (i.e., $>$3 lymph nodes measuring $>$3 cm or a single lymph node $>$7 cm), extranodal disease, cytopenia due to marrow involvement, spleen involvement (=16 cm by CT), leukemic phase, serous effusion, symptomatic or life endangering organ involvement, rapid lymphoma progression, consistently increased LDH levels. A policy of watchful waiting is not recommended in patients with Stage I–II disease, with the exception of patients with a short life expectancy due to severe comorbidity or with contraindications to therapy.

Issue 3: First line therapy (evidence–based recommendations)

In asymptomatic stage II–IV non bulky patients is rituximab alone better than watchful waiting? With the advent of rituximab and its relatively favorable side effect profile, a randomized trial compared watchful waiting with rituximab 375 mg/m^2 weekly for 4 consecutive weeks followed by rituximab maintenance every 2 months for 2 years [27] in 462 asymptomatic patients. Time for initiation of new therapy was significantly improved in the maintenance group in comparison with the watchful group: at 3 years 52 versus 9% of patients required treatment (HR, 0.20; 95% CI 0.13–0.29; $P = 0.001$). PFS was also significantly improved (81 vs. 33% at 3 years) by rituximab maintenance (HR, 0.21; 95% CI 0.15–0.29; $P = 0.001$). No statistically significant difference in OS was detected. Quality of life appeared to be ameliorated in patients receiving rituximab [28]. The panel agreed that improvement in long-term survival was the critical endpoint to be considered in this setting and that more evidence is needed before recommending rituximab in asymptomatic patients.

Recommendations For asymptomatic Stage II–IV, non bulky patients watchful waiting remains the standard of care and rituximab cannot be recommended (quality of evidence, low; strength of recommendation, weak).

In patients with stage I–II disease, which dose of radiotherapy is recommended? Involved field radiotherapy (IF-RT) remains the recommended treatment for patients with limited stage disease, as detailed in our previous guidelines [1]. A recent randomized trial compared 40–45 Gy with 24 Gy radiotherapy in 661 sites in patients with indolent NHL, predominantly follicular, reporting no difference in the major outcomes, which is response rate, PFS and OS [29].

Recommendations Patients with Stage I–II disease, a low tumor burden, and with documented contiguity of involved lymph-nodes treatable in the same radiotherapy field, should receive external involved field radiotherapy, at the dose of 24 Gy (quality of evidence, low; strength of recommendation, strong).

In patients with stage II–IV deserving treatment, is chemoimmunotherapy better than chemotherapy? Chemoimmunotherapy with rituximab was recommended for patients candidates to chemotherapy in our previous guidelines [1]. Four randomized trials [30–33] comparing chemoimmunotherapy with rituximab to chemotherapy without rituximab in naïve patients with FL Stage III–IV were selected. A pooled analysis was performed on the critical endpoints, that is, OS, failure free survival (FFS) and severe infections (Fig. 1). OS (HR, 0.59; 95% CI 0.44–0.79) and FFS improved (HR, 0.54; 95% CI 0.44–0.66). However, no relevant increase of severe infections was shown. Stage I–II patients with a high tumor burden were not enrolled into the above trials, but in absence of new evidence, the panel maintained the recommendation of the previous version of the guidelines [1], and agreed that patients with Stage II disease and high tumor burden, or FLIPI $>$2 should receive frontline chemoimmunotherapy.

Recommendations Patients with Stage III–IV should receive front-line chemoimmunotherapy. No evidence indicates chemoimmunotherapy in Stage II disease. However, the panel agreed that these patients should receive chemoimmunotherapy when there is high tumor burden or high-risk scoring system (quality of evidence, moderate; strength of recommendation, strong).

In patients candidates to frontline chemoimmunotherapy, which chemotherapy regimen should be chosen? Two randomized trials comparing different chemotherapy regimens associated with rituximab are available

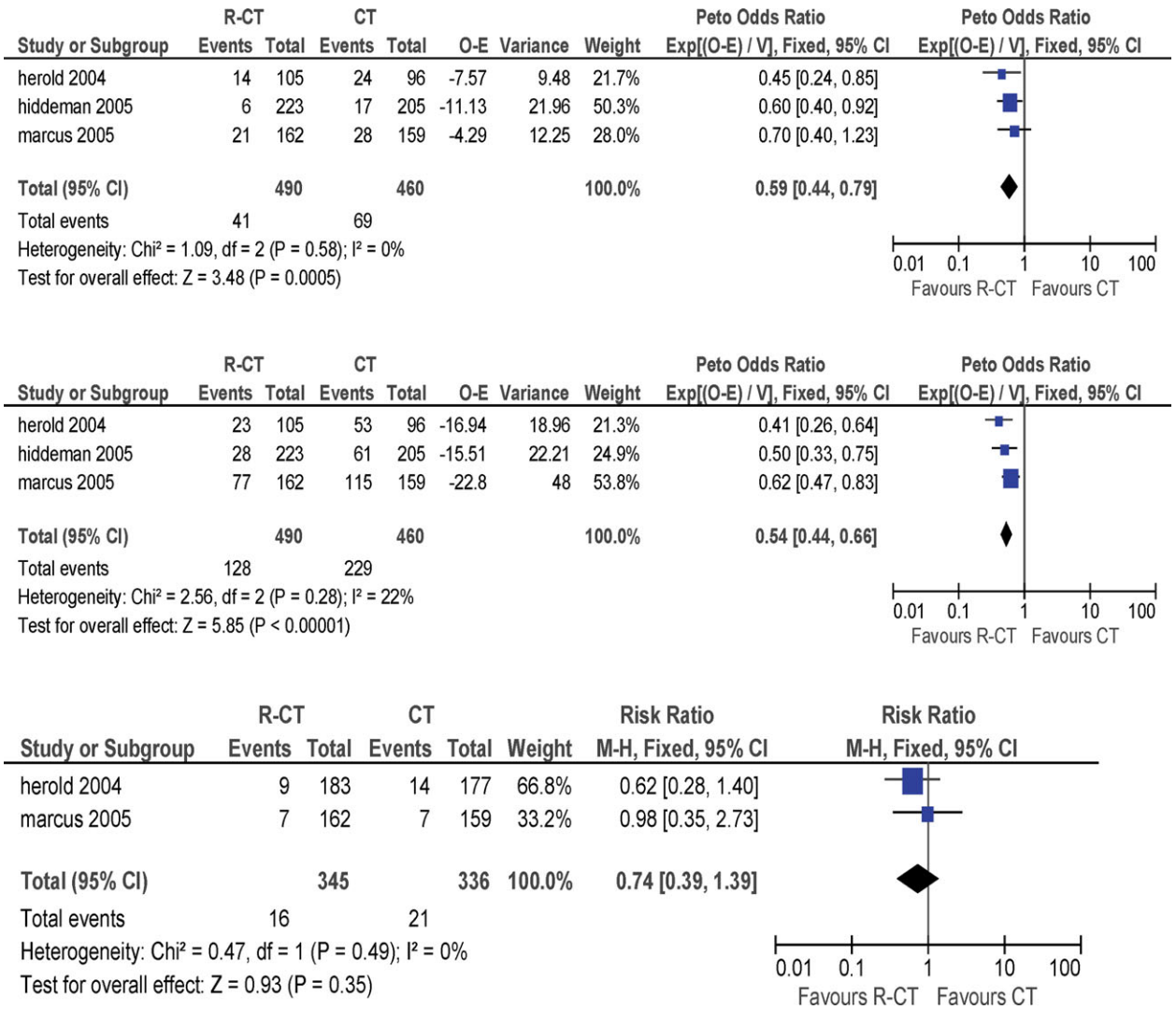

Figure 1. Result of the pooled analysis on the critical endpoints (overall survival, failure free survival, and severe infections) of the three published trials comparing chemoimmunotherapy with rituximab the chemotherapy without rituximab in patients with follicular lymphoma Stage III–IV. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

for analysis; however, both have been reported only in abstract form. Federico et al. in the FOLL05 trial compared R-CVP versus R-CHOP versus R-FM in a homogenous FL population of 534 patients [34]. A trend to longer 3 year PFS and a significant amelioration of time to treatment failure was noted in the patients treated with R-CHOP and R-FM. However, a higher rate of adverse events was shown with R-FM compared to the other two treatment schedules. A preliminary GRADE table could be built based on the data reported by the oral presentation. Rummel et al. tested R-bendamustine versus R-CHOP in a heterogeneous population of 513 patients, half of which had a FL while the remaining patients had a diagnosis of either mantle cell lymphoma or non-FL indolent lymphoma [35]. In the R-bendamustine group PFS was prolonged from 35 to 55 months compared to R-CHOP (HR, 0.57; 95% CI 0.43–0.77). Moreover, R-bendamustine had a lower rate of Grade 3–4 adverse events compared to R-CHOP. In elderly unfit patients several therapeutic options have been tested in phase II or retrospective studies: rituximab monotherapy, chlorambucil and rituximab, abbreviated chemoimmunotherapy. However, no randomized study is available to guide therapeutic decision. No GRADE table could be built based on the subset of data reported by the abstract.

Recommendations There is evidence that many frontline chemotherapy regimens, whether antracycline-based polychemotherapy (CHOP or CHOP like regimens) or fludarabine-based polychemotherapy, or CVP regimen or bendamustine can be used in association with rituximab (quality of evidence, low; strength of recommendation, weak).

In patients candidates to frontline chemoimmunotherapy, high-dose chemoimmunotherapy with autologous stem cell support is better than standard chemoimmunotherapy? The impact of high-dose therapy and autologous hematopoietic stem cell transplantation (HSCT) versuss conventional-dose chemotherapy in the management of FL has been faced by a systematic review of the randomized clinical trials addressing the question [36]. Seven trials proved eligible, four of which provided data from 941 patients that could be included in a meta-analysis and three of which remain unpublished. The results suggest that high-dose therapy and autologous SCT as part of FL initial treatment does not improve OS.

In the post-rituximab era, only one trial compared high-dose therapy and autograft with R-CHOP: 136 patients with untreated advanced FL Grades 1–3 were randomized either to six cycles of R-CHOP or to R-HDS schedule [37]. The R-HDS consisted of two cycles of APO regimen (dox-

orubicin, vincristine, and prednisone totaling 75 mg/sqm of doxorubicin administration); patients not achieving complete remission (CR) received two additional DHAP; the high-dose phase consisted of 2 g/sqm etoposide followed by two rituximab doses; afterwards 7 g/sqm of cyclophosphamide were delivered followed again by two rituximab doses; eventually mitoxantrone 60 mg/sqm and melphalan 180 mg/sqm followed by autologous HSCT were administered. CRs were 62% following R-CHOP and 85% following R-HDS ($P < 0.001$). Four years projected values for EFS were 28% for R-CHOP and 61% for R-HDS ($P < 0.001$). Four years projected values for PFS were 31% for R-CHOP and 68% for R-HDS ($P < 0.001$). OS was similar in the two arms (R-CHOP, 80%; R-HDS, 81%). The cumulative incidence of sMDS/AML at 4 years was 6.6% for R-HDS and 1.7% for R-CHOP ($P = 0.111$). A total of 26 non-fatal grades III to IV extra-hematologic early toxicities occurred in the R-HDS arm compared to a total of seven registered in the R-CHOP arm ($P < 0.001$).

Recommendation Upfront high-dose chemoimmunotherapy with autologous stem cell support cannot be recommended (quality of evidence, low; strength of recommendation, strong).

Issue 4: Assessment of response (consensus-based recommendations)

The independent prognostic significance of PET-CT performed at the end of induction therapy has been recently confirmed [38]; irrespective of conventional response [39], PET positivity was associated with a reduced PFS (33 vs. 71%) and an increased risk of death (HR, 7.0; $P = 0.001$). However, no study addressed the management of patients with discordant CT and PET results. Therefore, therapeutic decisions cannot be actually based on PET results. The prognostic role of molecular response is controversial, even though any residual positivity at the end of a rituximab containing program is associated with a remarkably poor outcome [21]. The prognostic role of BCL2/IGH levels after induction treatment still needs to be assessed in patients receiving rituximab maintenance.

Recommendations Clinical response to first-line therapy should be assessed according to revised IWG criteria [40]. Even though there is preliminary evidence that the best response evaluation includes PET, the panel did not reach a consensus on the extensive use of PET in response assessment. The panel agreed that PET could be indicated in patients in which the intention of therapy is achieving CR.

There is no evidence to support interim PET for guiding treatment decisions. PET is not recommended for routine use in the follow-up setting. The assessment of molecular response is not recommended for routine assessment.

Issue 5: Post-induction therapy (evidence-based recommendations)

In patients with at least partial response after first-line chemoimmunotherapy, is maintenance with rituximab better than watchful waiting? The panel agreed that improvement in PFS was the critical endpoint to be considered in this setting. The PRIMA study [41] randomized 1019 FL patients responsive to R-CHOP or RCVP to observation or rituximab maintenance (12 infusions of 375 mg/sqm given intravenously one every 8 weeks) starting 8 weeks after the last induction treatment. Three-year PFS was 74.9% (95% CI 70.9–78.9) in the rituximab maintenance group and 57.6% (95% CI 53.2–62.2) in the observation group (stratified log rank, $P = 0.0001$). The HR for risk of progression was significantly in favor for the rituximab maintenance group (HR, 0.55; 95% CI 0.44–0.68). Conversion from PR to CR was documented in 44% of the patients. No significant difference in mortality was reported in the two groups. Grades 3–4 adverse effects were 24% in the rituximab group and 17% in the observation group (RR, 1.46; 95% CI 1.14–1.87). Grades 3–4 neutropenia was 1% in the observation group and 4% in the maintenance group. Grades 3–4 infections were 1% in the observation group and 4% in the maintenance group. No statistical difference was documented in quality of life between the two groups.

Recommendations Maintenance therapy with rituximab is recommended in patients who reach at least a partial response at the end of first-line therapy (quality of evidence, high; strength of recommendation, strong).

In patients who achieved partial response after first-line chemoimmunotherapy, is consolidation with radioimmunoconjugates an option? Four hundred and fourteen patients were enrolled in a multicenter randomized trial (FIT trial) testing ibritumomab tiuxetan consolidation after response (PR or CR) to first-line chemotherapy in FL Stage III–IV compared to observation [42]. Radioimmunotherapy (RIT) consolidation converted 77% of patients who were in PR after induction therapy to CR ($P < 0.001$). After a median follow-up of 3.5 years, median PFS was 36.5 months in the RIT group and 13.3 months in the control group (HR, 0.465; $P < 0.0001$). At follow-up, there was no difference in OS between the two groups. Grades 3–4 infections were 8% in the RIT arm compared to 2.4% in the control group. The trial, however, enrolled only 15% of patients receiving rituximab as part of the induction regimen. This conclusion is further supported by several phase II studies where ibritumomab tiuxetan was given to patients after remission induction with R-CHOP [43,44] or FNR [45,46].

Recommendations Ibritumomab tiuxetan proved to prolong progression free survival in patients achieving partial response after first-line chemoimmunotherapy. However, the lack of comparison between ibritumomab tiuxetan and rituximab maintenance does not allow to produce recommendations on radioimmunotherapy in this setting (quality of evidence, low; strength of recommendation, weak). The panel claimed to be important to have a randomized study evaluating the role of radioimmunotherapy versus rituximab maintenance in patients who achieved a response after first-line chemoimmunotherapy.

Issue 6: Relapsed/refractory patients (evidence-based recommendations)

In patients relapsing after first line chemoimmunotherapy and requiring treatment, is rituximab and chemotherapy reinduction superior to chemotherapy alone? A trial randomized 465 FL patients relapsed after first-line chemotherapy not including rituximab to either R-CHOP or CHOP [47]. R-CHOP induction yielded an increased CR rate compared to CHOP therapy (CHOP, 15.6%; R-CHOP, 29.5%; $P > 0.001$). At a median follow-up of 33 months, patients treated with R-CHOP had significantly longer median PFS (33 vs. 20 months) from first randomization (HR, 0.65; $P < 0.001$). A slight non significant increase of Grade 3–4 neutropenia was reported in the R-CHOP arm (55 vs. 48%).

Recommendations In fit patients relapsing after first-line chemoimmunotherapy and requiring treatment, rituximab should be added to chemotherapy as reinduction, provided there is no evidence of resistance to rituximab (quality of evidence, low; strength of recommendation, weak).

In patients relapsing after first-line chemoimmunotherapy and achieving a response to reinduction rituximab and chemotherapy, is rituximab maintenance better than observation? Van Oers et al. [47] randomly assigned relapsing/resistant patients after R-CHOP or

CHOP to either observation or maintenance with single agent rituximab 375 mg/m^2 once every 2 months for a maximum of 2 years. When CHOP + rituximab was used for induction, the median PFS from second randomization for patients who received rituximab maintenance therapy was 4.4 years compared with 1.9 years (HR, 0.69; $P = 0.43$). When CHOP only was used for induction, these figures were, respectively, 3.1 years versus 1 year in the observation arm (HR, 0.37; $P < 0.001$). For patients in CR, median PFS was 4.4 years in the rituximab maintenance arm versus 1.2 years in the observation arm (HR, 0.48; $P = 0.003$). The last median follow-up [21] of 6 years showed that maintenance rituximab significantly improved median PFS (3.7 vs. 1.3 years; HR, 0.55), but was associated with a significantly higher rate of severe (Grades 3–4) infection (9.7 vs. 2.4%; $P = 0.01$). There was a non significant trend towards improved OS at 5 years with maintenance (74 vs. 64%; $P < 0.07$). Seven out of 167 patients withdrew from maintenance treatment because of toxicity: four had recurrent infections, one had severe neutropenia, one had ventricular arrythmia, and one had persistent general complaints. There were no deaths related to maintenance treatment. Three other randomized trials assessed rituximab maintenance in relapsed FL patients [48–50]. However, the studies enrolled patients with refractory FL, mantle cell lymphoma or other indolent NHL. Moreover, no chemotherapy reinduction was applied in two trials [49,50]. All the above studies were reported by a Cochrane systematic review [51]. Meta-analysis of the four available randomized trials reported that OS was significantly ameliorated (HR, 0.58; 95% CI 0.42–0.79) while also infection and severe infections were increased (HR, 1.99; 95% CI 1.24–6.76).

Recommendations In patients relapsing after first-line chemoimmunotherapy and achieving a response to reinduction rituximab and chemotherapy, rituximab maintenance is recommended (quality of evidence, low; strength of recommendation, weak).

Relapsed/refractory patients (consensus-based recommendations)

Which role for autologous HSCT? Two retrospective studies [52,53] analyzed the outcomes of patients treated with autologous HSCT or chemotherapy or chemoimmunotherapy in patients progressed or relapsed FL. Other cohorts assessed the role of autologous HSCT in rituximab pretreated patients [37,54–59]. The efficacy of rituximab prior to stem cell collection as in vivo purging has been tested by a randomized trial [60]. A retrospective analysis conducted by the Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) reported the results of addition of rituximab pre-HSCT [54]. Rituximab maintenance after autologous HSCT was also assessed [60]. Several design limitations restrict the applicability of the trial results to the indication of autologous SCT in patients relapsed or refractory. So the panel provided consensus based-recommendations.

Recommendations Autologous HSCT is recommended in young (<65-year old) fit patients relapsing within 12 months from the end of frontline chemoimmunotherapy and achieving a response to chemoimmunotherapy reinduction. Autologous HSCT is a therapeutic option in young (<65-year old) fit patients relapsing after at least 12 months from the end of frontline chemoimmunotherapy and achieving a response to chemoimmunotherapy reinduction. No sufficient evidence support universal rituximab maintenance in patients achieving a response after autologous HSCT.

Which role for allogeneic HSCT? Khouri [61] recently reported the 8-year experience with the fludarabine (30 mg/m^2 on days –5 –3), cyclophosphamide (750 mg/m^2 on days (3–5) and rituximab (375 mg/m^2 on day 13; 1,000 mg/m^2 on days –6, +1 and +8) (FCR) regimen in 47 chemosensitive FL patients treated with sibling donor ($n = 45$) or matched unrelated donor ($n = 2$). With a median follow-up of 60 months PFS and OS were 83% and 85%, respectively. Non relapse mortality (NRM) accounted for 15% of the patients. Pinana et al. [62] described the long term outcome of 37 FL patients with median age of 50 years (range 34–62 years) enrolled in two prospective protocols between 1999 and 2007. Patients with relapsed or refractory FL were treated with a conditioning regimen based on fludarabine (125–150 mg/m^2) combined with melphalan (80–140 mg/m^2). With a median follow-up of 52 months (range, 0.6–113 months), DFS at 4 years for patients with PD, PR or CR at transplantation were 29, 48, and 64%, respectively. The 4-year cumulative incidence of nonrelapse mortality were 71, 33, and 26%, respectively. Thomson et al. [63] reported the results of 82 consecutive patients with relapsed or refractory FL conditioned for allogeneic HSCT with alemtuzumab (20 mg on days –8 to –4) combined with fludarabine (30 mg/m^2 on days –7 to –3) and melphalan (140 mg/m^2 on day –2). With a median follow-up of 43 months the NRM was 15% at 4 years. Risk of relapse was 26%. At 4 years, the OS rate was 76%.

The EBMT Group reported a retrospective analysis on 44 matched unrelated donor stem cell transplantation (MUD-SCT) for relapsed or refractory FL. Compared to myeloablative conditioning regimens, RIC showed on multivariate analysis reduced NRM and significantly longer PFS and OS [64].

Hari et al. [65] compared retrospectively the outcomes of 208 FL patients (27–70 years) treated either with myeloablative conditioning ($n = 120$) or reduced intensity conditioning ($n = 88$) before an HLA-identical sibling allogeneic HSCT. There were no significant difference in 3-year PFS or OS between the two cohorts. On multivariate analysis, an increased risk of disease progression after RIC was observed (RR, 2.97, $P = 0.04$).

Recommendations Young (<65-year old) fit patients who relapsed after or were refractory to a previous therapy including autologous SCT are candidates to allogeneic SCT.

The availability of a compatible donor and the patient preference should be considered in making this decision

Which role for radioimmunoconjugates? The efficacy and safety of radiolabelled ibritumomab tiuxetan (single dose of 14.8 MBq/Kg) and tositumomab in patients with refractory/relapsed indolent NHL were compared with rituximab (375 mg/sqm once weekly for 4 weeks) and unlabelled tositumomab, respectively, in two randomized trials [66,67]. Response rates ranged from 55 to 86% and CRs were achieved in more than 30% of the patients. Higher response rates, longer TTP and fewer adverse effects were observed by retrospective analyses of patients receiving ibritumomab tiuxetan or tositumomab as a second line therapy versus third or further lines [68,69].

Recommendations The panel argued that for relapsed/refractory patients, treatment with radioimmunoconjugates is a therapeutic option. This should apply for those patients non eligible to high-dose chemotherapy and HSCT.

Discussion

At present, several treatments are available for FL but the information derived from literature may not fit with relevant clinical questions, and the endpoints and/or the population of patients included in trials are not always those relevant in the clinical practice. In this project, aimed at revising the guidelines for management of FL issued in 2005, we made specific evidence-based recommendations for the most relevant key issues according to the GRADE methodology, which imposes a preliminary judgment of the

TABLE I. Evidence-Based Guidelines for the Therapy of FL

	SIE (2012)	NCCN (2011) [69]	ESMO (2011) [71]	UK (2011) [70]
Staging PET	Useful to confirm limited stage candidates for IFRT and for baseline assessment when treatments are aimed at achieving CR	Useful in selected cases	Useful in rare cases, to Confirm Stage I–II	No routine use
BCL2	Not recommended for routine use	Useful under certain circumstance	NA	No routine use
FLIPI-1	Recommended, but it does not guide treatment decisions	Recommended for prognostic purposes	Recommended for prognostic purposes	Recommended
Frontline therapy Stage I–II	If contiguous lymph nodes: IFRT, 24-30 Gy; otherwise as for Stage III–IV	IFR,T 24-30 Gy Or immunotherapy +/– chemo +/–RT (observation in selected cases)	IFRT or EFRT, 30–36 Gy (observation in selected cases)	IFRT, 24 Gy
Stage I–II, high tumor burden	The same as stage III–IV	The same as Stage III–IV	The same as Stage III–IV	
Stage III–IV: criteria to start treatment	Symptoms (systemic, B); cytopenia due to lymphoma (marrow involvement, hematopoietic impairment); rapid/ steady lymphoma progression; threatened organ function/ compression. High tumor burden, spleen >16 cm; serous effusion; leukemic phase; consistently increased LDH levels.	Bulky disease	Bulky disease, serous effusion	Symptoms
Chemotherapy choice	Rituximab plus CHOP or CHOP-like, fludarabine-based; CVP, bendamustine.	Rituximab plus bendamustine, CHOP, CVP, fludarabine, FND RIT (category 2B)	Rituximab plus CHOP, CVP, FC or FM, bendamustine	Rituximab plus chemotherapy (no preferred regimen)
Alternatives to chemoimmunotherapy	Rituximab monotherapy not recommended except for selected elderly or unfit pts.	Rituximab monotherapy (or plus single alkylator): option especially for elderly and unfirm	Rituximab or radioimmunoconjugates monotherapy or chlorambucl plus rituximab	
Consolidation and maintenance				
Radioimmunotherapy	Recommended for pts achieving PR	Recommended	Recommended (prolonged PFS after chemoimmunotherapy unproven)	No routine use
Rituximab	Recommended	Recommended	Recommended	Recommended
Autologous HSCT	Not recommended upfront	Only second-line therapy	In clinical trials	Not recommended upfront
Relapse				
Chemotherapy	Including rituximab (if remission duration >6 months) plus noncross resistant agents	As first-line or FCMR	Rituximab if remission duration >6–12 months	Rituximab if R-naïve or R-responsive
Radioimmunotherapy	Recommended, especially in elderly or unfit pts	Recommended	Recommended for elderly pts or with co-morbidities or as consolidation	Recommended in the elderly and in those refractory or intolerant to chemotherapy
Autologous HSCT	Recommended for fit pts< 65 years, especially if remission duration <12 months	Recommended	Recommended, especially if short lived remission	To be considered balancing the benefits with the long-term risks
Allogeneic HSCT	Option for pts <65 years	Option for highly selected pts	Option for selected young pts	Option for younger pts with early relapse

[1]About 36 Gy onto bulky disease.
[2]It prolongs PFS but not OS.

quality of evidence and a subsequent assessment of the strength of the recommendation based on a qualitative risk-benefit analysis. Also other institutions recently produced or updated evidence-based guidelines for the management of FL (NCCN, BCSH, ESMO) [70–72] (Table I). Systematic reviews and consensus conferences addressed to specific therapeutic issues, such as HSCT [73] and radioimmunotherapy [74] have also been published. The majority of produced recommendations in our project are common to the above guidelines: in particular, several chemotherapy regimens are accepted for association with rituximab in frontline therapy of symptomatic advanced stage disease. In deciding the best frontline therapy, we grounded our decision on the resulting efficacy and safety evidence. However, the economic impact of frontline chemoimmunotherapy was also assessed in several studies, and R-CVP resulted cost-effective versus CVP [75–77], and R-CHOP versus CHOP [77]. Moreover, rituximab maintenance after chemoimmunotherapy was associated with an incremental cost per QALY gained of €12,600 to €18,147 versus R-CHOP followed by observation [78,79]. The guidelines issued in the last year, however, showed discrepancies about recommendations on radioimmunoconjugates and HSCT. Indeed, the available evidence for such therapies is low-level due to indirectness in available randomized studies and to lack of randomized studies. The results of ongoing trials investigating new therapeutic modalities and novel agents will probably modify the treatment management of FL in the next years. Thus, we have planned to update the present guidelines by the end of 2015.

Author Contributions

GB, ST, MM, and AB designed the research; MM and AB performed the systematic review of literature, graded the evidence, and prepared the summary tables of evidence. PLZ, AMC, ML, MM, AR, LR, CT, UV, and ST formed the panel of experts who discussed the summaries of evidence and produced recommendations. MM wrote the preliminary version of the paper. All authors participated in writing significant sections of the paper.

Acknowledgments

The SIE administered all aspects of the meetings. The funding sources had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.

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