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Current and future management of follicular lymphoma

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Abstract Follicular lymphoma is usually considered as incurable, but patient's outcome has been steadily improving over the last decade. The introduction of anti-CD20 monoclonal antibodies represented a major step. Treatment of patients should take into account accurate staging results, symptoms related to lymphoma, tumor burden, age and comorbidities. Several options are still available for patients with localized or asymptomatic low risk disease, and randomized studies should be developed for those patients. When a systemic therapy is needed, the combination of rituximab with a few of the available cytotoxic regimens clearly provides the best results. Rituximab maintenance appears to further improve the progression-free interval. Since most patients will likely survive for many years, the quality and duration of response as well as the short- and long-term side effects of the treatments should be carefully weighted during this prolonged therapeutic management.

Keywords Follicular lymphoma · Rituximab · Chemotherapy

Introduction

Follicular lymphoma is considered as the typical indolent lymphoma, with multiple therapeutic options available, but usually not curable when disseminated using standard therapeutic approaches. Although the median overall survival was in the range of 8–10 years at the end of the last century, patient clinical outcome has been dramatically improved in recent years. More than 70 % of the patients over the age of 60 may survive for at least 10 years, according to recent epidemiological projections [1]. The introduction of anti-CD20 monoclonal antibodies explains, in large part, this achievement. However, this disease is also characterized by a marked clinical heterogeneity; some patients being asymptomatic for many years, while others may rapidly present a life-threatening disease. The tumor burden criteria and the follicular lymphoma international prognostic index (FLIPI) may help to stratify patients for treatment decisions [2]. Furthermore, given the prolonged expected survival of patients with follicular lymphoma, it appears now critical to develop treatment strategies with limited impact on quality of life and without long-term toxicities (Table 1).

The management of follicular lymphoma patients with stage I disease

Patients with Ann Arbor stage I (or very limited stage II) disease may still represent 15–25 % of patients at diagnosis [3]. According to North American and European guidelines, the usual therapeutic recommendation, for those patients consists in localized radiation therapy [4, 5]. One randomized study comparing different doses of radiation indicated that 24 Gy may be optimal [6]. The long-term

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Table 1 Current unresolved clinical questions regarding the upfront treatment of follicular lymphoma patients

1. Patients with Ann Arbor stage 1
Is radiation therapy still the standard of care?
2. Patients with a low tumor burden
Is watchful waiting still an acceptable option in 2012?
3. Patients with a high tumor burden
Is there an optimal chemotherapy regimen to be combined with rituximab?

disease control achieved with this strategy has suggested that some patients may be cured with this approach [7]. However, retrospective series indicate that many patients do not receive radiation therapy, being either managed with observation (or watchful waiting, see below), with single agent rituximab, or with chemotherapy combined with rituximab and/or radiation therapy [4]. This could be related to the fear of toxicities associated with radiation therapy as well as the assumption that follicular lymphoma is always a disseminated disease with low levels of circulating lymphoma cells [8]. Unfortunately, there is a lack of systematic prospective or randomized study in this patient population, pre-empting the use of high level evidence-based recommendations. A recent analysis was performed in the United States, including 471 patients with stage I follicular lymphoma, and may help to optimize the management of this patients [9]. First, this study indicates that patients with incomplete staging (lack of bone marrow biopsy or complete scanning using CT or ^{18}FDG PET-CT) had an inferior outcome, emphasizing the need of rigorous patient check-up. Second, this study indicates that therapeutic approaches such as watchful waiting or single agent rituximab did not result in inferior results as compared to radiation therapy only. In fact, the best outcome was observed in patients receiving systemic treatment, either chemotherapy plus rituximab or combined modality approach (abbreviated rituximab chemotherapy followed by radiation therapy). Although this study is limited by its retrospective nature [9], these data clearly suggest that systemic treatments should be further evaluated in patients with limited stage follicular lymphoma patients.

The management of patients with disseminated disease and a low tumor burden

Given the indolent nature of the disease, the use of a watchful waiting strategy has been developed and further validated by randomized trials in the 90s. This approach has been limited to patients with precisely defined clinical characteristics usually defined as "low tumor burden" (Table 2). These studies have demonstrated that the use of systemic cytotoxic therapy could be safely delayed in these patients [10–12]. When rituximab became available, its favorable efficacy/toxicity ratio prompted investigators to evaluate either short or prolonged courses of the antibody in patients with a low tumor burden [13–15]. After 4 weekly infusions of rituximab, the response rate was about 70–80 %, half of those responders achieving a complete response. Although a few patients ($\sim$15 %) experienced a prolonged clinical and molecular response, median time to progression was usually <2 years [16]. Prolonged rituximab administration with 4 additional infusions or 2-year maintenance appeared to prolong response duration in 2 randomized studies [14, 17]. However, the ECOG E4494 RESORT study demonstrated that after the 4 weekly infusions, the time to rituximab failure or resistance was identical when rituximab was administered at lymphoma progression as compared to systematic rituximab maintenance [18]. Rituximab maintenance after rituximab single agent induction did not appear to increase patient quality of life [18, 19]. Moreover, the occurrence of side effects, especially infections, may constitute a burden (or even a

Table 2 Tumor burden criteria

These criteria can be used for selecting patients in which cytotoxic systemic therapy can be delayed. They are derived from studies performed by the Groupe d'Etude des Lymphomes de l'Adulte (GELA, by now called LYSA) [11] and the British National Lymphoma Investigators (BNLI) [12]

Criteria related to the tumor: patients should not present with:
Lymph nodes or tumor mass (except spleen) larger than 7 cm
Nodes greater than 3 cm in 3 distinct areas
Symptoms related to organ compression, pleural effusion or ascites, spleen enlargement; renal, liver or bone involvement
Biological criteria: patients should present with:
Serum LDH and serum beta2-microbulin below the upper normal values
Cytopenia (hemoglobin <10 g/dL or WBC <3.0 $\times$ 10^9/L or platelet counts <100 $\times$ 10^9/L) related to bone marrow infiltration
Criteria related to the effect of lymphoma on patient general status: patient should not present with
Systemic symptoms (fever, night sweats, weight loss)
Altered performance status (>1 on the WHO scale)
Time dependant related criteria:
Lack of generalized lymphoma progression over the last 3 months

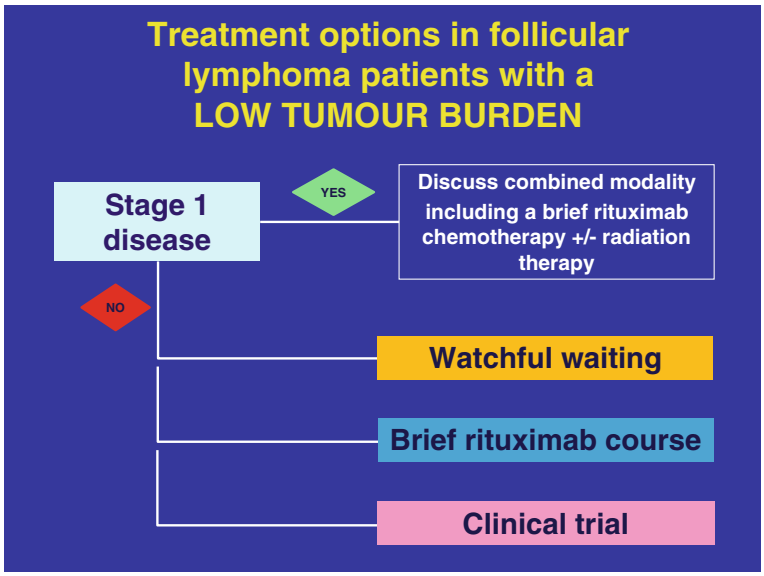

Fig. 1 This diagram summarizes the algorithm for patients with follicular lymphoma and a low tumor burden. If patients have a truly localized Ann Arabor stage 1 disease, a combined modality approach may be a suitable option. If the disease is disseminated, watchful waiting remains the standard option. Some patients may want to be treated with rituximab 4 weekly infusions, potentially followed by 4 infusions administered every 2 months; the benefit of long-term maintenance is not established. This population of patients may be also suitable for new strategies with non-cytotoxic agents within clinical trials

threat) too high for low tumor burden asymptomatic patients with an excellent prognosis.

Other approaches with the use of abbreviated therapy or radio-immunotherapy have also been developed in patients with a low tumor burden, but the results of these phase II non-comparative studies are difficult to interpret. Figure 1 describes an algorithm that can be used to help decision making in patients with a low tumor burden.

The management of patients symptomatic or with a high tumor burden

When patients with follicular lymphoma present with a high tumor burden or develop symptoms after a watchful waiting period, the use of cytotoxic chemotherapy combined with rituximab has been established as the standard of care in the last decade [20–23]. Several randomized studies have clearly demonstrated that this treatment improves response rates, progression-free and overall survival, as compared to chemotherapy alone. It was estimated that the risk of death was reduced by about 30 % in these patients with such strategies [24].

Different chemotherapy regimens have been evaluated in this context, such as R–CVP (rituximab, cyclophosphamide, vincristine, prednisone), R–CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone), R–bendamustine, or others. Until recently, the lack of comparative studies between these regimens precluded specific recommendations about their use, and choices were usually based on physician preferences or patient status. Data originating from the analysis of the different chemotherapy used in the PRIMA study, and two unpublished randomized trials enable us to draw several lessons:

- Retrospective analysis of patients receiving the R–FCM regimen (rituximab, fludarabine, cyclophosphamide and mitoxantrone) in the PRIMA study [25] as well as data originating from the FL-05 Italian study [26] regarding the R–FM regimen (rituximab, fludarabine, mitoxantrone), demonstrated that these fludarabine-containing regimens were as efficient as R–CHOP but significantly more toxic. This toxicity included severe infections and secondary neoplasia and the overall survival of patients was inferior to that achieved with other regimens.
- The response rates and progression-free survival associated with the use of R–CHOP were found to be significantly better than those observed with the use of R–CVP [25, 26]. However, so far, no study has demonstrated that the overall survival of patients was significantly better when R–CHOP was used. Indirect non-randomized data originating from the PRIMA study [25] or from the North American Lymphocare study [27] suggested, however, that R–CHOP may lead to a prolonged survival in patients with adverse features (those with a high FLIPI score, for instance).
- Finally, the German Stil NHL 1-2003 study compared the use of R–CHOP and R–bendamustine in patients with indolent lymphoma, and included 279 patients with

follicular lymphoma [28]. R–bendamustine appeared significantly less toxic than R–CHOP, with less hematopoietic, infectious and neurological toxicities. Furthermore, in patients with follicular lymphoma, complete response rates and progression-free survival were significantly better in the R–bendamustine arm. However, this benefit did not translate into an overall survival difference. It was also pointed by some investigators that the results obtained with R–CHOP in this trial were inferior to those of other studies [25, 26].

In conclusion, it seems that with the exception of fludarabine combination, at this time, the three R–CVP, R–CHOP and R–bendamustine regimens all appear to be acceptable options. Preliminary data indicate that R–CHOP should be preferred over R–CVP in patients with adverse prognostic features. In the wait for definitive results and confirmative studies, it might appear premature to conclude that R–bendamustine should always be preferred to R–CHOP, although the low toxicity profile of the former made it a very attractive option.

The role of consolidation after achieving a response to rituximab chemotherapy

Despite the efficacy of rituximab chemotherapy combinations, most patients will progress within 3–6 years after achieving a response to their induction regimen. Several studies have therefore attempted to consolidate remission using radio-immunotherapy or rituximab maintenance.

One randomized study evaluated the role of ^{90}Y-labeled ibritumomab tiutexan administration after chemotherapy [29]. The results indicated higher response rates and prolonged progression-free survival with the use of radio-immunotherapy. However, only a few patients had received rituximab in combination with chemotherapy before this treatment, indicating that it is difficult to extend these results in the modern treatment era. Furthermore, a higher number of secondary malignancies were observed with the use of radio-immunotherapy [30]. Another study compared the use of rituximab–CHOP versus rituximab–CHOP followed by the administration of ^{131}I tositumomab [31]. No significant differences were observed for progression free or overall survivals. Again, a slight excess of haematological malignancies was also observed after radio-immunotherapy. Altogether, these data indicate that radio-immunotherapy should be further evaluated for its efficacy and toxicity before it can be routinely used in the first line treatment of follicular lymphoma patients.

The role of rituximab maintenance in patients with follicular lymphoma responding to an induction immunochemotherapy has been evaluated in the PRIMA study [23]. Patients responding to R–CVP, R–CHOP or R–FCM were randomized to receive either one infusion of rituximab every 2 months for 2 years or no further treatment (observation). The risk of lymphoma progression was significantly reduced for those patients receiving maintenance rituximab (hazard ratio 0.55; 95 % confidence interval [CI] 0.39–0.64). Furthermore, a significantly higher proportion of patients (72 vs. 52 %; $P = 0.0001$) had reached a complete response 2 years after completing induction in the rituximab maintenance arm. The benefit of rituximab maintenance was observed whatever the patients' age, the quality of response after induction (complete vs. partial response) or the FLIPI groups, or the isoforms of the FcGRIIIA receptor [23, 32]. The best results with maintenance were also observed in patients that had received R–CHOP induction (3-year progression-free survival 70 vs. 60 % with R–CVP). However, no significant difference in term of overall survival was observed. Patients experienced more frequently adverse events during rituximab maintenance (24 vs. 17 % WHO grade 3/4 events, $P = 0.0026$) and more frequently infections, which were predominantly of grade 2. But only 4 % of the patients randomized in the rituximab maintenance arm withdrew from study for treatment-related toxicities.

A recent meta-analysis considering 9 studies and more than 2500 patients demonstrated that the use of rituximab maintenance was associated with a significant reduction of the risk of death (hazard ratio 0.76; 95 % CI 0.62–0.92) [33]. Although this findings were predominant in patients treated with rituximab maintenance in second line, a similar trend was observed for those receiving maintenance after first line treatment (hazard ratio 0.86, 95 % CI 0.60–1.25).

Usual management of patients with a high tumor burden is described in Fig. 2.

The management of patients at the time of lymphoma progression

When the first line treatment has failed, many options are available, including at least immunotherapy, chemo-immunotherapy, autologous or allogeneic transplant. Therapeutic decision should take into account patient age, fitness and priorities. Additional important considerations are: type of previous treatment, depth and duration of previous response and tolerability, as well histological transformation. This possibility should be systematically explored since it will prompt treatment strategies used in diffuse large B cell lymphoma.

Randomized studies performed at the time of progression have evaluated the use of rituximab maintenance after chemotherapy [34, 35], as well as the use of rituximab in the context of autologous transplant [36]. But treatment

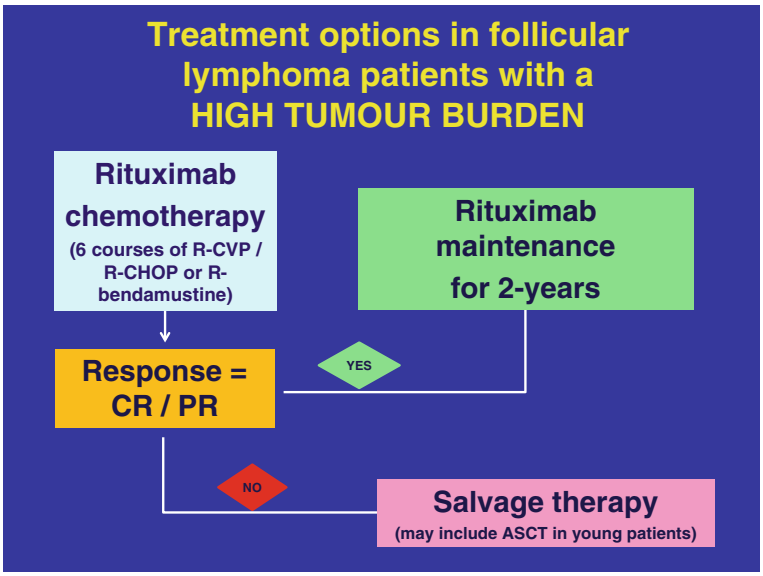

Fig. 2 In patients with a high tumor burden, the established standard of care is an induction treatment with a combination of rituximab plus chemotherapy, CVP, CHOP or bendamustine. If patients achieve a complete or partial response (CR or PR), then consolidation with rituximab maintenance is the treatment of choice. Patients not achieving a response to induction should be considered as poor prognosis patients and second line therapy with different regimen (or within clinical trials assessing new agents) should be proposed; this includes the possibility to plan autologous stem cell transplant (ASCT) in younger patients

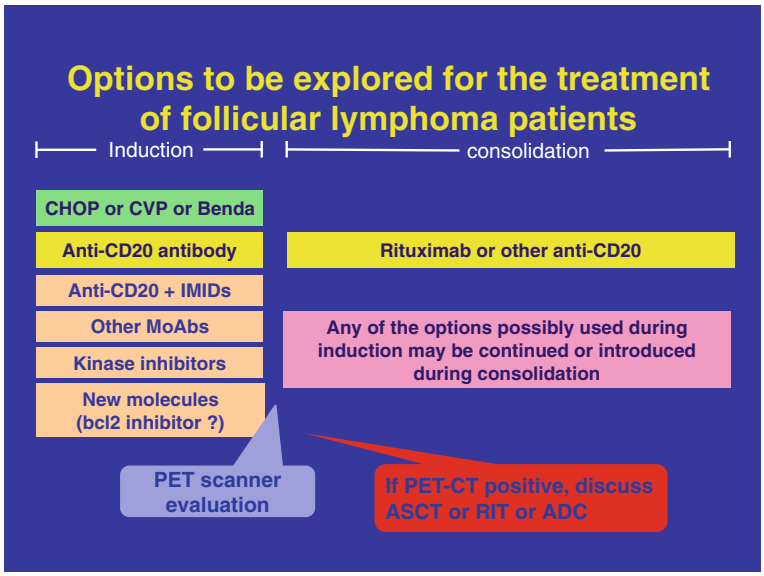

Fig. 3 This diagram describes several hypotheses to be explored to improve the treatment of follicular lymphoma patients. Given the benefit achieved with anti-CD20 antibodies, this part of treatment will probably remain a key component of the treatment during induction and consolidation. This can include rituximab or new generation anti-CD20 antibodies. The present chemotherapy combination may be challenged in the future by non-cytotoxic approaches such as the combination of rituximab plus IMIDs® or the combination of rituximab with new agents, new monoclonal antibodies (MoAbs), kinase inhibitors or bcl2 inhibitory molecules, for instance. These molecules may potentially be used during maintenance, either as continuation of induction therapy or being introduced after rituximab-chemotherapy induction. A thorough monitoring of response achieved after induction using PET–CT will likely be useful. It may identify patients who remain PET–CT positive after induction, in which other options such as autologous stem cell transplantation (ASCT), radio-immunotherapy (RIT) or new antibody drug conjugates (ADC) might be evaluated

strategies have not been compared, with the exception of a small underpowered study evaluating autologous transplantation [37].

The role of this latter option remains controversial [38], although several retrospective studies suggested its benefit, even the rituximab era [39, 40]. It is worth mentioning that the median progression-free survival achieved in the recent European Bone Marrow Transplant study of rituximab for induction and maintenance in the context of autologous transplant exceeded 5 years (in the rituximab containing arms) [36]. Such results are usually not attained using other options in the same setting.

Future perspectives and conclusions

Although many progresses have been made to understand the origin and biology of follicular lymphoma [41, 42], we are still essentially relying on clinical-related factors to guide our therapeutic decisions. We may hope that some biomarkers will provide useful insights into the future. Another field of interest is the monitoring of treatment efficacy, with the use of ^{18}FGD PET–CT. Recent retrospective and prospective studies demonstrated that PET–CT results can predict the outcome of patients at the end of induction immune-chemotherapy [43, 44].

Given the success of the first anti-CD20 antibody used, rituximab, several other antibodies targeting the same antigen are being developed, including ofatumomab, veltuzumab or obinutuzumab (also called GA101) [45]. This latter molecule is a new type II glyco-engineered humanized anti-CD20 recognizing a distinct epitope of this cell surface antigen. In in vitro and animal models, obinutuzumab was shown to have a very potent direct cell killing effect against malignant B cell, and an increased ability to induce antibody-dependent cellular cytotoxicity [46] Promising clinical data were obtained in phase I and II trials, suggesting a good safety and efficacy profile of this new antibody in follicular lymphoma patients [47]. The combination of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance is then currently being compared to the standard approach, rituximab plus chemotherapy induction followed by rituximab maintenance (GALLIUM study, NCT01332968). The use of immunomodulating agents to increase the efficacy of anti-CD20 antibodies has also been explored with very promising results [48], leading to the recent launch of a large international phase III study (RELEVANCE) testing this chemotherapy-free regimen against the standard rituximab-chemotherapy induction followed by rituximab maintenance (NCT01650701). Other new treatments are actively being developed with antibody drug conjugates or targeted therapies directed against key pathways involved in B cell signaling [49].

With all these options currently or soon to be available, one can imagine that multiple clinical studies will explore the different combination and strategies for the treatment of follicular lymphoma patients (Fig. 3). Finally, with the current therapeutic options available for patients with follicular lymphoma, which allow expecting a survival longer than 10 years for most patients, it becomes also crucial to consider short- and long-term treatment related toxicities, as well as patient age and comorbidities.

Firm data obtained in randomized clinical trials are available to choose some of our strategies for the benefit of the patients. But individualized therapy will become increasingly important with the new therapeutic tools in the future.

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