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EDITORIAL

Rituximab maintenance in follicular lymphoma patients

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Abstract

Rituximab maintenance (RM) therapy following successful induction has recently emerged as a highly effective treatment for follicular lymphoma (FL). Randomized trials analyzing the impact of RM compared to observation alone have demonstrated a significantly better outcome in terms of progression-free survival (but not overall survival) in patients (pts) who received as first-line treatment single-agent rituximab, standard chemotherapy (CVP) and recently also immunochemotherapy (R-CHOP, R-CVP or R-FND), as shown by preliminary results of the PRIMA trial. Also in the setting of relapsed disease, RM has shown significant benefit either after chemotherapy or immunochemotherapy. RM has been generally well tolerated, and treated pts developed only mild toxicity, mainly a small increased rate of neutropenia, hypogammaglobulinaemia and self-limiting upper-respiratory tract infections. Moreover, no cumulative or unexpected toxicities were observed and quality of life was not affected. These data have established RM therapy as an important part of multi-modal therapeutic strategies in patients affected by FL.

Key words: Follicular lymphoma; Immunochemotherapy; Maintenance; Rituximab

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INTRODUCTION

In last 10 years, the introduction of the chimeric anti-CD20 monoclonal antibody rituximab (R) has emerged as one of most important advances in the treatment of patients affected by B-cell non-Hodgkin's lymphoma (NHL), and especially diffuse large B-cell lymphoma and follicular lymphoma (FL). R selectively binds the CD20 surface antigen on B lymphocytes, and subsequently induces the killing of coated cells though a combination of different immuno-mediated effector mechanisms of action, namely complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and induction of apoptosis[1]. Although the efficacy of R was initially demonstrated when employed as a single agent[2], in patients affected by advanced FL the major benefits have been observed when combined with chemotherapy. In fact, as demonstrated in six randomized trials, the addition of R to every effective chemotherapeutic combina-

tion (CVP[3, 4], CHOP[5-7], CHVP[8], MCP[9] and FCM[10]), resulted in a significant increase in response rate, complete remission (CR) rate, progression-free survival (PFS) and even overall survival (OS) with respect to chemotherapy alone (Table 1), without relevant acute and long-term toxicities.

However, as indicated by continuous declination of PFS curves at long-term follow-up in these trials, relapses seem to continue after immunochemotherapy in these patients and none can be considered cured. Thus, eventual relapse remains an important clinical issue for the majority of patients with FL, and defining further ways to extend the period of remission remains an essential goal. An important way to achieve this goal is the concept of maintenance therapy, offering continued treatment to patients after successful induction therapy in attempt to prevent the re-emergence of disease. An early study of oral chlorambucil for 2 years demonstrated that this maintenance therapy was associated with significant prolongation of disease control, but without any improvement in OS[11]. For this reason, considering the adverse effects associated with prolonged exposure to alkylating agents, maintenance chemotherapy strategies were abandoned. The most extensively studied maintenance therapy for FL is the immunomodulatory agent interferon-alpha. A meta-analysis of 10 randomized studies which compared interferon-alpha maintenance with observation clearly demonstrated a significant improvement of 10% in the likelihood that patients would remain in ongoing remission at 5 years and 10 years ($P < 0.001$) and an 8% improvement in their likelihood of survival at 5 years and 10 years ($P = 0.004$) with interferon-alpha maintenance[12]. However, the adverse effects of prolonged interferon-alpha exposure and the resultant impairment of quality of life have resulted in this therapy being infrequently used in current clinical practice.

The ideal maintenance agent would have proven efficacy as monotherapy in FL, minimal acute and long-term toxic effects, simple administration, favourable treatment schedules, and require minimal monitoring of the patient. R has many of these characteristics and its use as a maintenance therapy for FL is very appealing. In particular, pharmacokinetic studies showed that R maintains a serum concentration considered active (25 g/mL) for a median time of 3-3.5 mo after infusion, suggesting that almost all patients would maintain this concentration with a dosing interval of 2 mo[13]. However, the optimal dosing schedule of RM has not been determined and the several phase II and randomized phase III studies performed so far have employed different maintenance schedules, mainly a single infusion every 2 or 3 mo for 2 years or 4 weekly administrations repeated at intervals of 6 mo for 2 years.

Considering the heterogeneity of maintenance schedules, of prior induction treatments, and the phase of disease in which maintenance is applied (onset or relapse), the goal of this editorial is to provide a comprehensive overview of RM, illustrating results after single agent R, after chemotherapy and after immunochemotherapy; in addition, we summarize infusional and late toxicity and the cost-effectiveness of R. We also provide discussion of alternative therapeutic strategies as consolidation after an induction treatment.

LITERATURE SEARCH

We searched PubMed (http://www.pubmed.gov) for articles with the keywords 'follicular lymphoma', 'rituximab', 'maintenance', and reviewed all references of the retrieved articles.

Abstracts from the American Society of Hematology, European Hematology Association and American Society of Clinical Oncology since 2007 were searched using the same keywords.

Overall, five major randomized studies have now published their final results on the role of RM in various clinical settings, either after single agent R[14-16], chemotherapy alone[17], or immunochemotherapy at relapse[6,7] (Tables 2 and 3). Preliminary results of a single large randomized trial (PRIMA, Primary R and MAintenance) investigating maintenance treatment after first-line immunochemotherapy have recently been reported[18]. Several of these studies also included patients with other forms of indolent lymphoma, but we will consider only data on the specific subset of patients with FL.

RITUXIMAB MAINTENANCE AFTER SINGLE AGENT RITUXIMAB

In one of the first studies evaluating RM, Hainsworth *et al*[16] randomly allocated patients responding to a previous standard 4-week course of R to receive either maintenance R given weekly for 4 wk every 6 mo for 2 years or R re-treatment (with the same schedule) at the time of lymphoma progression. The median PFS was 31.3 mo in the maintenance group compared with 7.4 mo in the re-treatment group ($P = 0.007$). However, the duration of R benefit (defined as the time to next anti-lymphoma treatment) was similar in the maintenance and in the re-treatment groups (31.3 *vs* 27.4 mo, P = NS); moreover, there was no difference in OS between the two cohorts (72% *vs* 68% at 3-years, P = NS).

Ghielmini *et al*[14] investigated maintenance R (a total of 4 infusions every 2 mo) following treatment with single-agent R in 202 patients with FL. The study was recently updated with long-term follow-up data (median 9.5 years)[19]. Overall, RM was associated with an improvement of 11 mo in median event-free survival (EFS) *vs* observation (24 *vs* 13 mo, $P < 0.001$). The best outcome was observed in previous untreated patients responding to R induction (8-years EFS 45% for the maintenance arm *vs* 22% for the observation arm; $P < 0.001$). In univariate analysis, baseline features predicting longer EFS were: disease diameter < 5 cm, being chemotherapy naïve, Ann Arbor stage lower than IV, and a VV phenotype at position 158 of the Fc gamma receptor RIIIA. At multivariate analysis, the only favourable prognostic factor for EFS was the maintenance treatment (HR 0.59, 95% CI 0.39

Table 1 Randomized trials comparing Rituximab-chemotherapy *vs* chemotherapy alone in follicular lymphoma patients

Reference	Year	Prior treatment	Treatment	No of patients	ORR	OS	PFS
Marcus *et al*[3, 4]	2005, 2008	No	R-CVP *vs* CVP	321	81% *vs* 57% ($P < 0.001$)	83% *vs* 77% at 4-years ($P = 0.029$)	27 *vs* 7 mo ($P < 0.001$) [1]
Hiddeman *et al*[5]	2005	No	R-CHOP *vs* CHOP	428	96% *vs* 90% ($P = 0.001$)	95% *vs* 90% at 2 yrs ($P = 0.016$)	91% *vs* 79% at 2 yrs ($P < 0.001$)[1]
van Oers *et al*[6, 7]	2006, 2010	Yes	R-CHOP *vs* CHOP	465	85% *vs* 72% ($P < 0.001$)	82% *vs* 79% at 3 years ($P = 0.09$)	33 vs 20 mo ($P < 0.001$)
Forstpointner *et al*[10]	2006	Yes	R-FCM *vs* FCM	125	95% *vs* 71% ($P = 0.01$)	Not available[2]	Not available[2]
Herold *et al*[9]	2007, 2010	No	R-MCP *vs* MCP	358	92% *vs* 75% ($P < 0.001$)	86% *vs* 74% at 5 years ($P = 0.02$)	86 *vs* 35 mo ($P < 0.001$)
Salles *et al*[8]	2000	No	R-CHVP-I *vs* CHVP-I	358	94% *vs* 85% ($P < 0.001$)	84% *vs* 79% at 5-years ($P = 0.15$)	53% *vs* 37% at 5 years ($P < 0.01$)

ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; [1]Time-to-treatment-failure; [2]Data not available because of protocol design (double randomization).

Table 2 Randomized trials comparing rituximab maintenance *vs* observation after single agent rituximab

Reference	Year	Prior treatment	Maintenance schedule	No. of patients	Median F-up	PFS	OS
Haisworth *et al*[16]	2005	R x 4 (weekly)	R x 4 (weekly) every 6 mo x 4 *vs* R x 4 weekly at relapse (retreatment)	62	41 mo	31.3 *vs* 7.4 mo ($P = 0.007$)	72% *vs* 68% at 3 years (P = NS)
Ghielmini *et al*[14] Martinelli *et al*[19]	2004 2010	R x 4 (weekly)	R every 2 mo x 4 *vs* observation	185	9.5 years	24 *vs* 13 mo ($P < 0.001$)	68% *vs* 54% ($P = 0.081$)

to 0.88, $P = 0.009$). Analysis of OS showed a borderline advantage for the maintenance arm (68% *vs* 54%; HR for death 0.63, 95% CI 0.37 to 1.06, $P = 0.0813$).

RITUXIMAB MAINTENANCE AFTER CHEMOTHERAPY OR IMMUNOCHEMOTHERAPY

The efficacy of RM therapy has also been investigated after treatment with different chemotherapy regimens. Hochster *et al*[17] randomly allocated 228 patients with previously untreated FL who had stable disease or better after CVP chemotherapy to either maintenance R (four weekly infusions every 6 mo for 2 years) or observation. Maintenance R was associated with greatly prolonged median PFS *vs* observation (4.3 years *vs* 1.3 years; $P < 0.001$) and borderline increased 3-year OS (91 *vs* 86%; $P = 0.08$). OS improved significantly only for patients with high tumour burden ($P = 0.03$).

In the setting of relapsed disease, two studies utilized a '2 X 2' factorial design to explore the benefits of the addition of R to multi-agent salvage chemotherapy, and also the role of RM. Forstpointner *et al*[10] randomly allocated patients with relapse of FL to FCM or R-FCM, followed by randomization to maintenance or observation. Response duration was longer with maintenance therapy (estimated median PFS not reached *vs* 16 mo in the observation group, $P < 0.001$); however, estimated OS at 3 years for the entire cohort, which also included patients affected by mantle cell lymphoma, was 77% in the group that received maintenance therapy and 57% in those assigned to observation ($P = 0.1$). Van Oers *et al*[6] randomly allocated pre-treated patients to CHOP or R-CHOP, with a secondary randomization to maintenance R or observation. In their initial report, at a median follow-up of 33 mo, maintenance therapy was associated with prolonged PFS (51.5 *vs* 19.4 mo $P < 0.001$) and with improved 3-yr OS (85.1 *vs* 77.1, $P = 0.011$). However, when follow-up was extended to 6 yrs, while the advantage of RM on PFS was confirmed (median 3.7 *vs* 1.3 years, $P < 0.001$), the beneficial effect on OS was not so evident (5-year OS 74% *vs* 64%, $P = 0.07$)[7]. This discrepancy might be partially due to the effect of the unbalanced use of R in the post-protocol salvage regimen. In fact, R was used most frequently in patients who had neither received R during induction treatment nor as maintenance.

An unplanned sub-analysis of 40 patients with relapsed FL who underwent RM after response to treatment with Fludarabine-R or Bendamustine-R in the context of the German Stil phase III NHL 2-2003 trial, showed that RM significantly prolonged OS and PFS[20]. Finally, in a large study 420 R-naïve patients were randomized to receive no R before and autologous stem cell transplantation (ASCT) (no R), R purging (weekly for 4 wk) before

Table 3 Randomized trials comparing rituximab maintenance *vs* observation after chemotherapy or immunochemotherapy

Reference	Year	Prior treatment	Maintenance schedule	No. of pts	Median F-up	PFS	OS
Hochster *et al*[17]	2009	CVP (1st line)	R x 4 (weekly) every 6 mo x 4 *vs* observation	228	3.7 years	Median: 4.3 *vs* 1.3 years At 3 years: 64% *vs* 33% ($P < 0.001$)	At 3 years: 91% *vs* 86% ($P = 0.08$)
Forstpointner *et al*[10]	2006	FCM or R-FCM (relapsed disease)	R x 4 (weekly) every 6 mo x 2 *vs* observation	105	26 mo	Median: Not reached *vs* 16 mo ($P < 0.001$)	At 3 years (estimated): 77% *vs* 57% ($P = 0.1$)
van Oers *et al*[6, 7]	2006 2010	CHOP or R-CHOP (relapsed disease)	R every 3 mo x 8 *vs* observation	334	6 years	Median: 3.7 *vs* 1.3 years At 3 years: 59% *vs* 28% ($P < 0.001$)	At 5 years: 74% *vs* 64% ($P = 0.07$)
Salles *et al*[18, 23]	2010	R-CHOP, R-CVP, R-FCM (1st line)	R every 2 mo x 12 *vs* observation	1018	25 mo	At 2 years: 79% *vs* 60% ($P < 0.001$)	At 2 years: NS

high-dose therapy BEAM conditioning (Rp), RM after ASCT (every 3 mo for 2 years) (RM) or both (Rp + RM). At a median follow-up of 6.4 years, 5-year PFS was 62.9% for patients receiving Rp + RM *vs* 37.6% for patients receiving no R ,while 5-yr OS was not different[21].

META-ANALYSIS

In 2009 a meta-analysis of the five randomized controlled trials[6, 10, 14, 16, 17] that compared RM therapy with observation or R at relapse was performed[22]. Data for 985 patients with FL were available for the meta-analysis of OS. Patients treated with maintenance R had statistically significantly better OS than patients in the observation arm or those treated at relapse (HR for death = 0.60, 95% CI= 0.45 to 0.79). Patients with refractory or relapsed disease had a survival benefit with maintenance therapy (HR for death = 0.58, 95% CI= 0.42 to 0.79), whereas previously untreated patients did not (HR for death = 0.68, 95% CI= 0.37 to 1.25). There was no significant difference between patients treated with different maintenance schedules (i.e. 4 weekly infusions every 6 mo or a single infusion every 2-3 mo). These results strongly support the benefit of RM in the setting of relapsed disease after successful induction therapy. A recent update of this meta-analysis, including the published extended follow-up data of previous studies and the data of an additional 2 trials[21,23] (2283 patients), confirmed all the previous conclusions (significant improvement in OS in the whole cohort and in relapsed/refractory patients with, no significant benefit on OS in previously untreated patients and a significant improvement in PFS in every group of patients)[24].

RITUXIMAB MAINTENANCE AFTER FIRST-LINE IMMUNOCHEMOTHERAPY

The role of R as maintenance therapy following first-line immunochemotherapy was addressed by the PRIMA trial, whose preliminary results were recently reported at American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) 2010 Congresses[18], and updated with an additional year of follow-up at the 2010 American Society of Hematology meeting[23]. The PRIMA trial is an international effort conducted by the French Group d'Etude des Lymphomas de l'Adulte (GELA) in 223 centres from 25 countries in untreated FL (grade 1, 2 and 3a) patients requiring therapy. Induction consisted of R for 8 infusions combined with either CHOP for 6 cycles, CVP for 8 cycles, or FCM for 6 cycles. Patients responding to induction therapy were subsequently randomized to either maintenance R 375 mg/m^2 every 2 mo for 24 mo or observation. A total of 1217 patients were enrolled in the study, with 1,018 patients randomized after a response (CR/PR) to induction treatment. FLIPI risk groups were as follows: low risk 21%, intermediate 36%, and high risk 43%. R-CHOP was used in 75% of patients, R-CVP in 22% and R-FCM in 3%. CR/Cru was obtained in 71% of patients and PR in 29%. After a median follow-up of 36 mo, RM therapy reduced the risk of lymphoma progression by 45% (hazard ratio = 0.55, 95% CI=0.44 –0.68, $P < 0.001$), with 2-year PFS of 79% in RM (n = 505) compared to 60% in observation (n=513). Subgroup analysis demonstrated improvements across all age categories, FLIPI risk scores, induction chemotherapy choice, and response to induction chemotherapy. The magnitude of risk reduction was greater for patients in PR (55% risk reduction) than in CR/CRu (48% risk reduction). The risk of requiring next anti-lymphoma treatment or chemotherapy was reduced by 40% with maintenance R. Adverse events were more frequent in the maintenance R arm, including grade 3-4 adverse events in 24% compared to 17%; grade 3-4 neutropenia and infection both occurred in 4% compared to less than 1%. There was no increase in deaths related to treatment arm and quality of life was not diminished with RM. In summary, the PRIMA trial demonstrates that addition of maintenance R every 2 mo for 2 years following first-line immunochemotherapy resulted in a significant improvement in PFS with acceptable toxicity. The follow-up time was too short to see any improvement in OS.

The British Columbia Cancer Agency (BCCA) reported a retrospective population-based analysis of 251 patients affected by FL, who were treated between 2004 and 2010 with first-line R-CVP, since 2006, patients responding to induction treatment, underwent RM (every 3 mo for 2 years). At a median follow-up of 3 years, PFS was signifi-

Table 4 Toxicities in trials comparing rituximab maintenance *vs* observation in follicular lymphoma

Reference	No of. patients	Grade 3-4 AE	Neutropenia (grade 3-4)	Grade 3-4 Infections
Haisworth *et al*[16]	62	9% *vs* 4%	2% *vs* 0%	0
Ghielmini *et al*[14]	185	28% *vs* 20%	18% *vs* 17%	NA
Martinelli *et al*[19]				
Hochster *et al*[17]	228	NA	3% *vs* 1%	1% *vs* 1%
Forstpointner *et al*[10]	105	NA	13% *vs* 6%	4% *vs* 3%
van Oers *et al*[6]	334	NA	10.8% *vs* 5.4% (P = 0.07)	9% *vs* 2.4% (P = 0.009)
Salles *et al*[18, 23]	1018	23% *vs* 16%	4% *vs* 1%	4% *vs* 1%

cantly improved in patients receiving RM compared to patients on observation alone, while OS did not, also confirming in a population-based approach the data of clinical trials[25].

MOLECULAR BASIS

Few and still controversial data have been published on the benefit of RM based on molecular status (persistence or disappearance of Bcl2/IgH positivity in bone marrow and/or peripheral blood) after induction treatment. The only study that investigated this topic found no difference in PFS in patients who were Bcl2/IgH positive or negative before beginning RM, which conversely determined improvement in outcome regardless of pre-maintenance molecular status[26]. However, some criticisms have been raised in this study: first of all, only major breakpoint rearrangement (MBR) has been investigated and, most importantly, patients with unknown molecular status (not informative for Bcl2/IgH rearrangement) were included in the group without evidence of blood and marrow involvement[27].

TOXICITY

Several concerns regarding the prolonged use of R have been raised and evaluated. The first issue is the prolonged B-cell depletion associated with this clinical practice. As discussed before, based on pharmacokinetic analysis and assuming a R serum level of 25 mcg/mL for maintaining B-cell depletion[13], the single infusion of R every 2-3 mo appears to be the most appropriate. However, this schedule produces the maximum B-cell depletion, and the increased risk of low immunoglobulin levels alongside with possible additional infectious complications remain a concern. In the study by van Oers *et al*[6], patients in the RM arm had a median IgG level of 6.3 g/L, compared with 7.3 g/L in the observation arm. Maintenance was omitted in two patients with IgG levels < 3 g/L. Another side effect reported with the use of R is the development of neutropenia (Table 4). In the same trial, neutropenia was reported in 10.8% of patients in the R arm compared with 5.4% in the observation arm (P = 0.07). The increased incidence of hypogammaglobulinaemia and neutropenia may both have contributed to an increased rate of grade 3-4 infection (9% *vs* 2.4%, P = 0.009), most of which were in the ear-nose-throat area. Six patients were hospitalized; however, they all fully recovered and there were no deaths related to RM. Based on cumulative data reported in three trials, the previously cited meta-analysis confirmed that patients who underwent RM therapy had more infection-related adverse events than patients in the observation arm (RR=1.99, 95% CI= 1.21 to 3.27). When only grade 3 or 4 infection-related adverse events were included in the analysis, this effect was even more pronounced (RR 2.90, 95% CI=1.24 to 6.76)[22].

The phase Ⅲb study MAXIMA, specifically evaluated the safety of RM (every 2 mo for 2 years) given either as the standard infusion rate or as a rapid infusion (≤ 90 min) in FL patients (first-line 395 patients, relapsed/refractory 150 patients) responding to induction treatment. The full course of RM was completed by 407 patients (58 patients discontinued due to progression, 16 patients due to toxicity). R-related adverse events were reported in 57 patients, the most common being infections (22 patients)[28].

On the other hand, in an analysis of 215 patients from Memorial Sloan-Kettering Cancer Center, hypogammaglobulinaemia was registered in 39% of patients with normal baseline levels following exposure to R, and 10% needed intravenous immune globulin replacement for symptomatic hypogammaglobulinaemia[29].

COST-EFFECTIVENESS OF MAINTENANCE

The cost-effectiveness of R in the treatment of patients with FL is an important issue[30]. Regarding the cost-effectiveness of RM, after induction therapy *vs* current standard practice (observation), a lifetime transition model was developed[31] based on PFS and OS obtained from the EORTC 20981 trial. The results tend to show that RM therapy may be a cost-effective strategy in the management of relapsed/refractory FL patients, at least in France. The cost of R was partly offset by the lower cost of relapse due to a longer time in the disease-free health state for patients in the R arm. An analysis concerning the cost-effectiveness of first-line RM in patients with untreated FL has been reported in the perspective of the UK National Healthcare Service[32]. Based on evidence from the PRIMA trial, the simulation of incremental cost-effectiveness ratios (ICERs) demonstrated that the superior clinical benefits of first-line RM are sufficient to justify the additional costs over observational practice.

ALTERNATIVE STRATEGIES

An alternative consolidation strategy could be the use of radioimmunotherapy (RIT). Morschhauser and colleagues[12] have reported results of the FIT trial: in this study patients who entered first remission with chemo-

therapy or immunochemotherapy were randomized to ^{90}Y ibritumomab or to observation. There was a significant improvement in the failure-free survival rate for RIT consolidation in patients who had received induction therapy with only chemotherapy. Nevertheless, RIT may be an attractive consideration in elderly patients where anthracycline induction is not desired and the burden of every-8-week therapy for 2 years is too much.

DISCUSSION

RM has emerged in recent years as a very appealing therapeutic strategy in patients affected by FL responding to induction treatment, as all randomized trials concordantly demonstrated that this practice is safe, has an acceptable toxicity profile and significantly improves response duration and PFS. However, many features of this topic have not yet been fully elucidated and have to be critically discussed. First of all, every single trial was unable to support a significant OS benefit, even after considerable follow-up. Probably the main reason for this is that patients with FL retain sensitivity to chemo-immunotherapy for long periods and those who did not undergo RM could often be effectively rescued with salvage R-containing treatments.

Although the meta-analysis recently published demonstrated a survival benefit for maintenance treatment, especially in relapsed patients, the limitations of this type of analysis that pool data obtained in different settings of patients (first-line or relapsed, R naïve or not), treated with different induction regimens (R alone, chemotherapy alone, or chemo-immunotherapy) cannot permit definitive conclusions. Moreover, none of the studies comprised in the meta-analysis explored the effect of RM after the first-line current standard of care in patients affected by FL, i.e. immunochemotherapy. For this reason the striking preliminary data of the large international PRIMA study on RM after frontline immunochemotherapy (R-CVP, R-CHOP, R-FM), that confirmed the efficacy of this strategy on PFS (with halved risk of relapse at 2-years) without any relevant toxicity, seem to open the door to the acceptance of this strategy as a new standard of care[18]. However, other alternative post-induction consolidation strategies, such as radio-immunotherapy[12], have been developed and demonstrate an improvement in PFS similar to that of PRIMA, albeit with a chemotherapy only induction approach in the majority of patients: for these reasons future studies directly comparing these different options are needed. Moreover, a new generation of monoclonal antibodies, such as the new anti-CD20 monoclonal antibody GA-101, is now coming from the bench to the bedside, and could eventually be incorporated in future maintenance strategies.

At the present time, the best chemotherapy regimen in combination with R in first-line treatment (CHOP, CVP, FM or Bendamustine) is not known, and it is not clear whether RM could have different efficacy after different immuno-chemotherapeutic regimens. Some ongoing trials are trying to address these issues.

Another important issue is that the best schedule (4 weekly infusions every 6 mo or a dose every 2 or 3 mo) and the optimal duration of RM (8 mo, 2 years or until progression) has not been determined, as the different schedules and treatment durations have not been directly compared. An ongoing Swiss study is comparing 2 years *vs* 5 years of maintenance: preliminary safety data after a median maintenance time of 3.3 years seem to suggest that RM beyond 2 years is feasible without evidence of increased toxicity, even if it is too early to draw definitive conclusions about the safety of RM administered beyond 2 years[33].

In conclusion, RM has shown to be effective and well tolerated in the majority of patients. Current available results of randomized trials support the benefit of RM in all relapsed patients responding to 2nd line treatment and not candidates for intensive approaches (autologous stem cell transplantation) and this strategy has been approved by regulatory organisations in many countries. Finally, preliminary results of the PRIMA study seem to open the door to incorporate RM after successful induction immunochemotherapy in the comprehensive standard 1st line therapeutic strategy for patients affected by advanced FL requiring treatment. Definitive data of the PRIMA trial and future comparative studies with other alternative post-induction consolidation or alternative maintenance strategies (i.e. with new monoclonal antibodies), are ultimately needed to define the standard of care in the near future for untreated patients affected by FL.

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