Management Strategies for Follicular Lymphoma patients in Remission after Modern Frontline Chemoimmunotherapies

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Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma [1]. The development of rituximab represented a major breakthrough in the management of FL, with several landmark clinical trials consistently demonstrating superior survival outcomes with rituximab-containing chemoimmunotherapies compared to chemotherapy alone, both in the frontline [2-5] and relapsed/refractory settings [6]. However despite the remarkable advances in chemoimmunotherapy for FL, these modalities are still not considered curative, hence; strategies designed to extend remission duration is often a key therapeutic goal. Nearly all FL patients treated with first line chemoimmunotherapies will eventually relapse. The currently available options to extend the duration of first remission and possibly survival outcomes in FL include; consolidation with autologous transplantation, maintenance rituximab (MR), radioimmunotherapy (RIT) consolidation and rituximab retreatment (RRT). In this editorial we provide a brief overview of how to approach a patient with FL in remission following first line modern chemoimmunotherapies.

Five randomized clinical trials have examined the role of autologous transplantation for consolidating FL patients in first remission, both in the pre-rituximab [7-10], and rituximab eras [9]. Unfortunately; while none of these trials were able to demonstrate an overall survival (OS) benefit with autologous transplantation, this modality was associated with a significantly higher risk of secondary myelodysplastic syndrome, acute myeloid leukemia [7], and second malignancies [10]. While keeping in perspective the recent advances in the management of FL including RIT consolidation [11], MR [12], or RRT [13], the routine use of autologous transplantation for FL in first remission is not recommended, especially considering its associated risk of secondary malignancies, and the lack of a clear OS benefit.

Several prospective studies have evaluated the role of MR for FL patients in remission after frontline therapies (Table 1). The ECOG (Eastern Cooperative Oncology Group) 1496 trial randomized 311 indolent NHL patients after frontline chemotherapy with cyclophosphamide, vincristine and prednisone to either MR or observation [14]. MR in this study was associated with a longer progression-free survival (PFS) but no OS advantage was seen. However; since patients in the ECOG 1496 study did not receive rituximab in combination with induction chemotherapy, the results of this trial cannot be extrapolated to patients receiving rituximab-containing induction chemoimmunotherapies. The role of MR in patients receiving rituximab-based induction chemoimmunotherapies was addressed in the recently published PRIMA study [12], where MR when compared to observation alone, was associated with higher response rates, improved PFS, but no OS benefit [12]. It is important to note that MR in PRIMA study was not able to improve quality of life (QOL). In the preliminary results of Italian Lymphoma Foundation (ILF) trial, a brief course of MR after a fludarabine-based chemoimmunotherapy induction was not able to significantly prolong PFS, when compared with patients in the observation arm [15]. The short rituximab maintenance schedule used in ILF study is likely responsible for this lack of PFS benefit. Considering the collective data summarized in table 1, in FL patients responding to frontline induction chemoimmunotherapies, MR appears to be a reasonable option. When offering this therapy to a potential patient the associated healthcare costs, possible increase in adverse events, and the lack of an OS benefit or improved QOL must be taken into consideration.

A potential alternative to MR is re-treatment with rituximab at the time of relapse. Potential advantages of a retreatment strategy include administration of fewer rituximab doses, potentially lower healthcare costs, and possibly fewer infectious complications. The ECOG recently presented the preliminary results of the RESORT trial in the 2011 annual meetings of American Society of Hematology [13]. The RESORT study was designed to compare MR against RRT in the frontline setting. In this study 284 FL patients responding to four weekly doses of rituximab were randomly assigned to either MR or RRT at progression (four weekly rituximab doses). At a median follow-up of 3.8 years, time to treatment failure (defined as disease progression within 6 months of the last rituximab dose) was not significantly different between the two arms (3.9 years for MR vs. 3.6 years for RRT).

Author (Year)  No. of patients  Maintenance schedule  PFS or EFS (MR vs. Observation)  OS (MR vs. Observation)
Hoehster 2009 [14] 387  Four weekly doses every 6 months for 2 years  64%* vs. 33% (3 years)  91%* vs. 86% (3 years)
Martineilli 2010 [16] 202  Single dose at 3, 5, 7 and 9 months  24 months* vs. 13 months  Difference not statistically significant
Sailes 2011 [12] 1217  Single dose every 2 months for 2 years  75%* vs. 58% (3 years)  Not significantly different between the two arms
Vitolo 2011 [15] 242  Single dose every 2 months for 4 doses  80% versus 68% (2 years)  No data available

Abbreviations: MR: Maintenance Rituximab; OS: Overall Survival; PFS: Progression-free Survival
*Statistically significant value

Table 1: Maintenance of rituximab in patients with follicular lymphoma after frontline therapies

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While significantly more patients in the MR arm were free of cytotoxic chemotherapy at 3 years (95% vs. 86%), this was achieved at the cost of three times greater use of rituximab in the maintenance cohort. Most importantly MR was not able to demonstrated better QOL, reduced anxiety, or fewer infectious complications. The remarkable findings of RESORT trial that RRT maintains patient QOL, and that it is associated with significantly less rituximab use has important ramifications for current clinical practice. At our specialized Myeloma and Lymphoma Service at the West Virginia University, we prefer RRT over MR for FL patients (particularly the subset with low bulk disease) following frontline immune- or chemoimmunotherapies.

Another option, with the potential to extend remission duration in FL is RIT consolidation (e.g. with yttrium-90-ibrutinumab tiuxetan (Zevalin)). In randomized study of 414 FL patients, RIT consolidation with Zevalin significantly prolonged median PFS (36.5 v 13.3 months in control arm), but without any clear OS benefit (11). The most common toxicities with RIT were hematologic and grade 3 or 4 infections. No randomized studies to our knowledge have compared RIT against MR or RRT in FL. Since administration of RIT is typically only feasible in academic medical centers or larger private practices equipped with nuclear medicine facilities capable of handling radioisotopes/biohazards, and also secondary to the relatively long neutrophil nadirs following Zevalin therapy, widespread use of this consolidation modality is limited in current clinical practice.

The outcomes of patients with FL have dramatically improved over the last decade, owing mainly to the addition of immunotherapy with rituximab in the therapy armamentarium. Ongoing clinical trials in the coming years will hopefully clarify the pros and cons of longer (>4 years) and shorter (<1 year) MR schedules, compared to the standard 2 year schedule used currently (NCT00877214 and NCT00227695; www.clinicaltrials.gov). Whether the results of maintenance therapy can be improved by incorporating chemo- or immunotherapeutic agents also warrants prospective investigation. The ongoing ECOG 2408 protocol is examining the role MR with or without lenalidomide in newly diagnosed FL (NCT01216683). Continued prospective trials in the coming years will hopefully clarify the best therapeutic modality for FL in first remission after frontline chemoimmunotherapies.

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