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Hot Topic

Pros and cons of rituximab maintenance in follicular lymphoma

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ABSTRACT

Follicular lymphoma (FL) is the most prevalent indolent non-Hodgkin lymphoma. Most patients present with advanced disease and are incurable with current therapy. The approval of rituximab has revolutionized the treatment of follicular lymphoma when administered in the induction setting for high-tumor burden disease, but the use of rituximab as a maintenance therapy (MR) continues to be a point of controversy. In this article, we review the main data and arguments in favor and against MR in FL. In summary, most studies have demonstrated a significant benefit in progression-free or event-free survival in this notoriously recurrent disease; however, long-term outcomes could not consistently demonstrate to be improved with this intervention. In a meta-analysis of randomized trials overall survival (OS) showed a tendency to improvement when given to patients in relapse, but no single study reached a significant OS advantage. The risk of high-grade transformation does not seem to be reduced in prospective trials. On the other hand, MR clearly increases toxicity without an improvement in quality of life. Finally, MR is expensive, and it is not proven that the delayed relapse time can compensate for these costs. In conclusion, despite the proven increase in progression-free survival, MR can't be recommended as a standard for the treatment of FL.

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoproliferative disorder in western countries; it is considered incurable because of frequent relapses despite excellent responses to currently available therapies. The duration of subsequent remissions decreases progressively over time, and the disease ultimately becomes resistant to treatment or transforms into high-grade aggressive lymphoma.

The anti-CD20 monoclonal antibody rituximab, which has high affinity for normal B-cells and the majority of B-cell lymphomas, brought significant improvement in the treatment of FL, increasing response rate, progression free survival (PFS) and overall survival (OS) when added to the first-line or relapsed regimens [1,2]. Mainly thanks to rituximab, the median survival of FL patients increased from 10 to 15 years in the past two decades with only a slight increase in self-limiting toxicity [3,4].

As patients with FL almost inevitably relapse, the temptation is high to try to prolong this remission by administering a maintenance treatment. Maintenance can be defined as continued treatment beyond induction therapy while in remission. The ideal maintenance strategy would involve significant benefit, good tolerance, minimal side effects, and convenient administration. In the past decades, maintenance therapy over a period of 12–24 months was evaluated using cytotoxic agents such as chlorambucil, cyclophosphamide [5] or interferon-α [6]. However, prolonged administration of either chemotherapy or interferon-α did not provide consistent long-term benefit in terms of OS, and were further limited by toxicity and patient inconvenience. As rituximab has the advantages of a relatively safe profile and prolonged half-life it is an optimal agent to evaluate as maintenance for FL.

Several trials investigated maintenance rituximab (MR) using a variety of schedules and following different induction regimens, such as single-agent rituximab, chemotherapy, or rituximab and chemotherapy combinations. No data hitherto suggest that one schedule is superior to another. The two most common schedules are one dose every 2 or 3 months for 1–2 years, or to administer four weekly infusions every six months for 1–2 years. The latter modality uses approximately twice as much drug with apparently no better effect. According to a retrospective comparison, one infusion every 2 months could be more toxic than one infusion every 3 months, without increased efficacy [7]. Concerning duration, the SAKK 35/03 trial indicates that a long-term administration up to 5 years does not significantly improve event-free survival

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(EFS) and is associated with increased toxicity compared to a short-term schedule of four administrations every 2 months.

The clinical impact of these maintenance strategies was investigated in several prospective randomized clinical trials in various settings of FL, including relapsed and previously untreated disease (Table 1). Given the absence of direct evidence indicating an OS benefit of MR, debates about its merit in FL are still ongoing. In this article, we review the main data available for MR in FL and the arguments in favor and against it.

Arguments favoring MR

MR prolongs PFS and EFS

MR after single agent rituximab

Although single agent rituximab is well tolerated and obtains a high response rate, the proportion of complete responses (CR) and the duration of response are lower compared to chemotherapy. In an effort to optimize the efficacy of single agent rituximab, Hainsworth et al. [8] investigated an extended rituximab therapy by administering first-line treatment with scheduled maintenance at 6 months intervals. This study reported a CR and overall response rate (ORR) higher than expected with induction only (37% and 73%, respectively), as well as a prolonged median PFS of 34 months. In a randomized phase III trial, the clinical benefit of extended rituximab administration was further confirmed by Ghielmini et al. Untreated and relapsed FL patients who responded to standard single agent rituximab induction or with stable disease were randomly assigned to prolonged rituximab administration (4 additional doses of rituximab at 8-week intervals) or observation [9]. At a median follow-up of 9.5 years, the median EFS was 24 months in MR arm versus 13 months in the observation arm with no relevant increase in toxicity; the subgroup of previously untreated patients obtained the most benefit from MR, with 8-year EFS of 45% [10]. However, the optimal duration of MR maintenance after single agent R induction remains unknown. The SAKK 35/03 trial randomizing 1 year versus 5 years of MR could not demonstrate a significant increase in EFS (main endpoint), although PFS was significantly increased (secondary endpoint) from 3.5 years to 7.4 years but was associated with increased toxicity [11].

MR after chemotherapy

MR significantly improves PFS in FL patients responding to induction chemotherapy without rituximab. In the phase 3 Eastern Cooperative Oncology Group (ECOG) 1496 trial, untreated FL patients undergoing CVP induction were randomized to MR or observation (Table 1). MR significantly increased the 3-year PFS and prolonged the median PFS compared with observation: 4.8 vs 1.3 years (HR = 0.49, $P < 0.001$) at a median follow-up time of 11.5 years, with an acceptable safety profile compared to observation. The improvement of PFS was independent of tumor burden, histology grade, degree of residual disease and Follicular Lymphoma International Prognostic Index (FLIPI) [12]. In the phase III EORTC 20891 trial, relapsed and refractory patients with FL were randomized to R-CHOP or CHOP as the induction treatment; patients responding to induction were further randomized to MR or observation (Table 1). After CHOP induction, the 6-year follow-up demonstrated that MR can significantly improve the median PFS (3.1 vs 1.0 years; HR = 0.37, $P < 0.001$) [13].

MR after R plus chemotherapy

The EORTC 20891 trial demonstrated that in relapsed and refractory FL patients MR treatment considerably improves PFS not only after CHOP but also after R-CHOP induction. [13] At 6-year follow-up the advantage in PFS after R-CHOP induction was

Table 1
Randomized Phase III trials on clinical efficacy of maintenance rituximab in follicular lymphoma.

Study	Setting	N	Induction	Schedule	Duration	Follow-up time	EFS/PFS MR vs OB	OS MR vs OB
SAKK 35/98, 2010	Untreated/Relapsed	202	R wk × 4	Once every 2 months	8 months	9.5 years	Median EFS 24 vs 13 months ($P < 0.01$)	None
ECOG 1496, 2016	Untreated	282	CVP	Once wk × 4 every 6 months	2 years	11.5 years	Median PFS 4.8 vs 1.3 years ($P < 0.0001$)	10-year 67% vs 59% ($P = 0.69$)
PRIMA, 2013	Untreated	1217	R + Chemo	Once every 2 months	2 years	6 years	6-year PFS 59.2% vs 42.7% ($P < 0.0001$)	None
EBMT, 2013	Relapsed	280	R + HDC-ASCT	Once every 2 months	8 months	8.3 year	10-year EFS 54% vs 37% ($P = 0.012$)	10-year 73.1%vs 67.8% (P = NS)
EORTC 20981, 2010	Relapsed	462	CHOP ± R	Once every 3 months	2 years	6 years	Median PFS 3.7 vs 1.3 years ($P < 0.001$)	5-year 74% vs 64% ($P = 0.69$)
GLSG, 2006	Relapsed FL/MCL	125 (FL)	R + FCM	Once wk × 4 at 3 and 9 months	9 months	26 months	None	3-year 77% vs 57% ($P = 0.1$)

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; EFS, event-free survival; FCM, fludarabine, cyclophosphamide, and mitoxantrone; MCL, mantle cell lymphoma; MR, maintenance rituximab; n, number of patients; OB, observation; OS, overall survival; PFS, progression-free survival; R, rituximab; wk, weekly; y, years.