Maintenance rituximab after autologous stem cell transplantation in patients with mantle cell lymphoma

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Background: High-dose therapy and autologous stem cell transplantation (ASCT) improves outcomes for patients with mantle cell lymphoma (MCL), but relapse ultimately occurs in most patients. Recently presented interim results from a phase III prospective trial suggest maintenance rituximab (MR) after ASCT for MCL improves progression-free survival (PFS). The maturation of these data and any benefit of MR on overall survival (OS) remain to be defined.

Patients and methods: In this retrospective study, we examined a cohort of consecutive patients with MCL that underwent ASCT for MCL at our center and evaluated their outcomes according to whether they received MR after ASCT ($n = 50$) or did not ($n = 107$). MR was treated as a time-dependent covariate to account for variation in timing of its initiation.

Results: MR was associated with an improved PFS [hazard ratio (HR) 0.44; confidence interval (CI) (0.24–0.80), $P = 0.007$] and overall survival (OS; HR 0.46; CI 0.23–0.93, $P = 0.03$) following a multivariate adjustment for confounding factors with a median follow-up of ∼5 years. Grade 4 neutropenia was increased (34% versus 18%, $P = 0.04$) in the MR group, but no effect on the rate of mortality unrelated to relapse was observed.

Conclusions: These data support that MR after ASCT for MCL confers a benefit in PFS and additionally suggest it may improve OS. General application of this strategy will require confirmation of benefit in prospective randomized trials.

Key words: mantle lymphoma, autologous transplantation, rituximab, maintenance

introduction

Mantle cell lymphoma (MCL), a mature B-cell non-Hodgkin lymphoma (B-NHL), typically presents with disseminated nodal and extra-nodal involvement, and a variable but aggressive course. Treatment strategies depend on patient age, condition, and preference [1]. Patients fit to receive intensive treatment may benefit from multi-agent immunochemotherapy followed by consolidation with high-dose therapy and autologous stem cell transplantation (ASCT) [2–4]. Despite an objective response rate (ORR) exceeding 90% in recent series [5, 6], patients almost inevitably relapse and not all are candidates for intensive therapy, necessitating improvements in standard treatment [4].

Increasingly, data support a role for the administration of maintenance therapy for improving outcomes after induction. In patients with MCL unable to receive ASCT consolidation, maintenance rituximab (MR) after induction immunochemotherapy has been shown to extend progression-free survival

(PFS) [7, 8] and overall survival (OS) [9, 10]. For patients with MCL that undergo ASCT, however, the value of MR after ASCT remains to be established, though limited retrospective data have shown a benefit in PFS [11] and recently presented interim data from a prospective phase III trial indicate an improvement in PFS, but not OS [12]. In this article, we analyze the impact of MR following ASCT in a sequential cohort of patients with MCL treated at our institutions.

methods

study cohort

We retrospectively studied consecutive patients with MCL who underwent ASCT at the University of Washington Medical Center (UWMC), the Fred Hutchinson Cancer Research Center (FHCRC), and the Veterans Affairs Puget Sound Health Care System (Seattle, Washington) between November 1995 and May 2011. Data were collected from comprehensive medical record review and institutional databases. Follow-up was updated as of November 2014. MR was defined as rituximab administered after ASCT in the absence of disease progression. Patients who underwent tandem autologous/allogeneic stem cell transplantation ($n = 2$) or had inadequate data to assess receipt of MR ($n = 5$) were

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excluded from analysis. All authors had access to the primary clinical data. The Institutional Review Board of FHCRC approved data collection and analysis.

treatment and definitions

Transplant conditioning regimens were determined based on patient age, co-morbidities, remission status, and prior therapies and categorized as chemo-therapy-only or radiation-based. Chemotherapy-only regimens consisted of busulfan, melphalan, and thiotepa as well as carmustine, etoposide, cytarabine and melphalan . Radiation-based regimens included fractionated total body ir-radiation (TBI) combined with cyclophosphamide with or without etoposide or high-dose radiolabeled antibody-based regimens either alone or in combin-ation with cyclophosphamide and etoposide or combined with fludarabine. Rituximab maintenance regimens are described below in the Results section.

Response to chemotherapy was defined as chemosensitive if a CR or a partial remission (PR) had been achieved with the chemotherapy immediately before ASCT according to standard criteria [13, 14]. Simplified MCL prognostic index (sMIPI) scores were calculated using data from diagnosis and before ASCT [15].

statistical methods

Patient characteristics and treatments were compared using a χ^2 analysis or Fisher's exact test, as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test. PFS and OS were calculated from the date of ASCT, where PFS was defined as a lack of relapse, progression, or death from any cause.

To account for the variability in time to its initiation after ASCT, MR was treated as a time-dependent covariate. Statistical significance of differences in event rates between the MR and no-MR groups was evaluated with the Cox proportional hazards regression model. The number of events of the outcome in PFS and OS was sufficiently small to require a selection process for covariate inclusion. Covariates were selected according to clinical rele-vance and by using a series of univariate models to pare down the possible variables that would be useful, then backwards selection was employed to determine which variables would be included in the model. Two-sided P-values less than 0.05 were considered statistically significant.

Treating MR as a time-dependent covariate prohibits the precise graphical de-piction of the data since patients move from the no-MR group to the MR group at different points after ASCT [16]. Survival curves were therefore approximated using Kaplan–Meier (KM) plots generated with a day 100 landmark; patients who died or experienced progression of disease before day 100 after ASCT were not included in the KM plots and patients who did not begin MR before day 100 remained in the no-MR group. Statistical differences in the survival curves were estimated using the Cox proportional hazards regression model.

results

patient characteristics

One-hundred and fifty-seven patients met the above criteria and were evaluated in this study. Their demographics and characteristics are summarized in Table 1. The median age at ASCT was 57 years old (range 35–71) and 134 (85%) were men. MR was administered to 50 patients (32%) and the remaining 107 patients (68%) received no MR. Patients in the MR and no-MR groups were similar with respect to gender, age, blastoid-variant histology, and the presence

Table 1. Demographic and clinical characteristics of study cohort, stratified by receipt of maintenance rituximab

Variable	All ($n = 157$)	MR ($n = 50$)	no-MR ($n = 107$)	P-value[a]
Male (%)	134 (85)	41 (82)	93 (87)	0.47
Median age at ASCT (range)	58 (35–71)	58 (38–71)	58 (35–70)	0.43
B-symptoms at diagnosis (%)	39 (25)	16 (32)	23 (21)	0.17
Blastoid variant (%, of evaluable)[b]	12 (9)	2 (4)	10 (11)	0.16
sMIPI at diagnosis[b] (%, of evaluable)				
0–2	37 (31)	14 (36)	23 (28)	
≥3	84 (69)	25 (64)	59 (72)	0.38
Chemosensitive disease (%)	144 (92)	49 (98)	95 (89)	0.06
Rituximab before ASCT (%)	144 (92)	50 (100)	94 (88)	0.01
HiDAC with induction (%)	58 (37)	25 (50)	33 (31)	0.02
sMIPI at ASCT[b] (%, of evaluable)				
0–2	79 (51)	27 (54)	52 (50)	
≥3	76 (49)	23 (46)	53 (50)	0.61
ASCT in the first remission (%)	98 (62)	42 (84)	56 (52)	<0.001
Disease status at ASCT (%)				
CR	74 (47)	34 (68)	40 (37)	
PR	68 (43)	13 (26)	55 (51)	
SD/Relapse	15 (10)	3 (6)	12 (11)	0.002
Transplant conditioning (%)				
Chemotherapy-only	35 (22)	19 (38)	16 (15)	0.001
Radiation-based	122 (78)	31 (62)	91 (85)	
Year of ASCT (%)				
1995–2003	47 (30)	8 (16)	39 (37)	0.009
2004–2011	110 (70)	42 (84)	68 (64)	

MR, maintenance rituximab; ASCT, autologous stem cell transplant; HiDAC, high-dose cytarabine; sMIPI, simplified mantle cell lymphoma international prognostic index; CR, complete remission; PR, partial remission; SD, stable disease.
[a]P-values are calculated from comparing the MR and no-MR groups.
[b]Data are not available for all patients.

of B-symptoms at diagnosis. All patients in the MR group had received rituximab before ASCT, whereas 13 of the 107 patients in the no-MR group had no prior rituximab ($P = 0.01$). Patients in the MR group were more likely to have received high-dose cytarabine as a component of induction chemoimmunotherapy ($P = 0.02$) and to have undergone ASCT during first remission ($P < 0.001$) and in complete remission (CR) ($P = 0.002$), and to have received conditioning without radiation ($P = 0.001$). The groups were well matched for sMIPI score at the time of diagnosis ($P = 0.38$) and at ASCT ($P = 0.61$). Patients who received MR underwent ASCT more recently than those patients that did not ($P = 0.009$).

maintenance rituximab regimens

The decision to administer MR was made by the treating physician on an individual basis ($n = 150$) or as a part of two separate phase II protocols ($n = 7$). MR was given according to the following dosing schedules: weekly dosing for 4 weeks every 6 months for two to four courses ($n = 15$), weekly dosing for a single 4-week course ($n = 8$), and every 3-month dosing for two to eight doses ($n = 7$); multiple different dosing schedules were used in the remaining cases ($n = 20$). A median of eight (range 1–16) doses of MR was administered at a dose of 375 mg/m^2. MR was initiated at a median of 77 days after ASCT (range 27–287, standard deviation 56 days) and the last dose was administered at a median of 271 days after ASCT (range 55–1074).

toxicities of maintenance rituximab

Grade 4 neutropenia was observed in 16 of 47 assessable patients (34%) in the MR group, and 16 of 87 assessable patients (18%) in the no-MR group ($P = 0.04$). Granulocyte colony stimulating factor (GCSF) was administered for neutropenia in 15 of 47 assessable patients (32%) in the MR group, and 10 of 85 assessable patients (12%) in the no-MR group ($P = 0.005$). Mortality unrelated to MCL relapse (NRM) occurred in four patients (7%) in the MR group and

nine patients (9%) in the no-MR group ($P = 0.77$) at a median time of 840 days (range 7–2730) after ASCT, and no instances of NRM were predated by documented severe neutropenia.

association of maintenance rituximab with PFS and OS

Direct unadjusted comparison of PFS and OS between the MR and non-MR groups indicated a PFS (HR 0.48; CI 0.29–0.82, $P = 0.007$) and OS (HR 0.43; CI 0.23–0.80, $P = 0.008$) benefit was associated with MR (Supplementary Table S1, available at *Annals of Oncology* online). Since the decision to deliver post-transplant MR was non-randomized, we evaluated these end points in the context of the baseline features of each treatment arm. Following multivariable analysis adjusting for potentially confounding variables, the association of MR with a significantly prolonged PFS (HR 0.44; CI 0.24–0.80, $P = 0.007$) (Table 2) was retained. Multivariable analysis was similarly carried out to account for imbalances potentially impacting OS, and MR retained its association with improved OS (HR 0.46; CI 0.23–0.93, $P = 0.03$) (Table 2) with a median follow-up after ASCT for surviving patients of 5.0 years (range 0.02–18.1).

As the study spanned a range of time during which the treatment options for MCL evolved to include novel agents such as proteasome inhibitors and immunomodulators, we conducted additional analyses to identify whether the OS benefit with MR might reflect the use of these newer treatment options. Patients who relapsed after ASCT were entered into a Cox proportional hazard model of OS after relapse. The same covariates as shown in Table 2 were included. There was no difference in OS after relapse (HR 1.3 for MR group, $P = 0.75$), implicating time to progression (TTP) after ASCT as the key factor influencing OS. Additionally, as the cohort of patients that underwent ASCT between 2004 and 2011 reflects a population treated according to more modern algorithms, it was examined independently with an

Table 2. Multivariate analysis of factors imbalanced between the MR and no-MR groups

Variable	PFS (91 events)		OS (67 events)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
MR	0.44 (0.24–0.80)	0.007	0.46 (0.23–0.93)	0.03
Year of ASCT[a]	1.16 (1.06–1.27)	0.001	1.03 (0.93–1.14)	0.50
Chemosensitive disease	0.43 (0.22–0.87)	0.02	0.41 (0.19–0.88)	0.02
ASCT in 1st Remission	0.43 (0.26–0.71)	<0.001	0.36 (0.20–0.65)	<0.001
CR at ASCT	0.49 (0.28–0.85)	0.01	0.51 (0.27–0.96)	0.02
Chemo-only conditioning	0.76 (0.44–1.30)	0.32	0.74 (0.40–1.39)	0.36
Rituximab before ASCT	0.73 (0.26–2.01)	0.54	0.51 (0.20–1.34)	0.17
sMIPI ≥3 at ASCT	2.49 (1.43–4.33)	0.001		
B symptoms at diagnosis	2.42 (1.40–4.20)	0.002		

The Cox proportional hazard model for PFS included the following variables: the year of ASCT, receipt of rituximab before ASCT, disease status at ASCT, chemosensitivity, whether ASCT was carried out in 1st CR, the conditioning regimen, presence of B-symptoms at diagnosis, and the sMIPI score at the time of ASCT. The Cox proportional hazard model for OS included the following variables: the year of ASCT, receipt of rituximab before ASCT, disease group at ASCT, chemosensitivity of disease, whether ASCT was carried out in the first CR, and the transplant conditioning regimen. Note the relatively smaller number of events registered for OS compared with PFS precluded inclusion in the model of the presence of B-symptoms at diagnosis and the sMIPI score at the time of ASCT.
PFS, progression-free survival; OS, overall survival; MR, maintenance rituximab; ASCT, autologous stem cell transplant; sMIPI, simplified mantle cell lymphoma international prognostic index; CR, complete remission.
[a]Continuous variable.

interaction analysis for OS. This showed no association of the time period of ASCT with the effect of MR on OS ($P = 0.36$).

With the limitations described above for graphically representing estimates of survival in time-dependent covariate analyses, PFS and OS at 3 years were 79% and 91%, respectively, in the MR group and 55% and 69%, respectively, in the no-MR group (Figure 1).

Since ASCT consolidation is now thought most beneficial to patients with MCL in first CR (CR1) or first PR (PR1), inter-action analyses were carried out for this subgroup, as well. These showed no relationship between remission status of disease at ASCT ($P = 0.26$ for PFS and 0.92 for OS) or whether ASCT was carried out in the first remission ($P = 0.49$ for PFS and 0.93 for OS) and the effect of MR on survival outcomes, indicating that the benefit of MR in this setting is not impacted by remission status and holds true for this most clinically relevant setting. Kaplan–Meier plots of the CR1/PR1 subgroup using a day 100 landmark are shown in Figure 2. Though the limitations of plot-ting these time-dependent covariate data reduce the power of the observations when shown graphically, the impact of MR in this subgroup is best described by the interaction analyses that suggest its benefit meets statistical significance.

discussion

MR after ASCT in patients with MCL has to-date shown potential though not conclusive benefit, though all previously published prospective studies have included small numbers of representative patients and have been non-comparative [17–20]. The data pre-sented here suggest that MR after ASCT for patients with MCL results in an improvement in both PFS and OS. The relatively large number of patients evaluated ($n = 157$), long follow-up (median = 5 years), comparative nature, and detailed information allow for adjustment for many potential imbalances inherent to the retrospective analysis. The relative effect-size for each end point after multivariable adjustment (HR 0.44; CI 0.24–0.80, $P = 0.007$ for PFS; HR 0.46; CI 0.23–0.93, $P = 0.03$ for OS) are comparable with those demonstrated in a prospective rando-mized study comparing MR versus maintenance interferon alfa in patients with MCL that received R-CHOP induction therapy (HR 0.41; CI 0.26–0.65, $P = 0.0001$ for remission duration; HR 0.48; CI 0.23–0.97, $P = 0.04$ for OS) but were not fit enough to subsequently undergo consolidative ASCT [10].

The benefit to OS shown here for patients receiving MR after ASCT is in contrast to a retrospective analysis from Dietrich
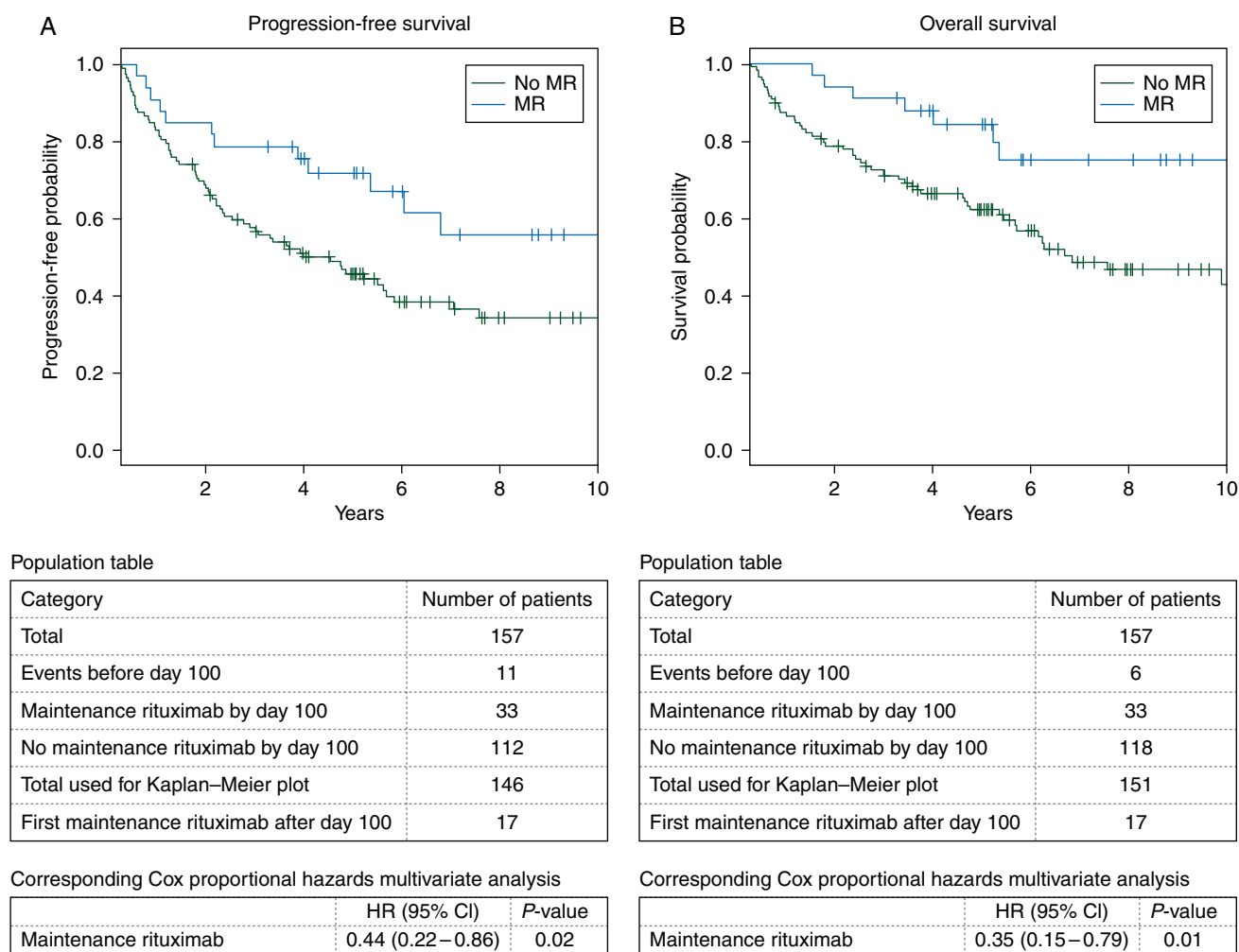

A Progression-free survival

B Overall survival

Population table

Category	Number of patients
Total	157
Events before day 100	11
Maintenance rituximab by day 100	33
No maintenance rituximab by day 100	112
Total used for Kaplan–Meier plot	146
First maintenance rituximab after day 100	17

Population table

Category	Number of patients
Total	157
Events before day 100	6
Maintenance rituximab by day 100	33
No maintenance rituximab by day 100	118
Total used for Kaplan–Meier plot	151
First maintenance rituximab after day 100	17

Corresponding Cox proportional hazards multivariate analysis

	HR (95% CI)	P-value
Maintenance rituximab	0.44 (0.22 – 0.86)	0.02

Corresponding Cox proportional hazards multivariate analysis

	HR (95% CI)	P-value
Maintenance rituximab	0.35 (0.15 – 0.79)	0.01

Figure 1. Kaplan–Meier plots using landmark of day 100 after autologous stem cell transplant depict the effect of MR on PFS (A) and OS (B). The population tables describe the number of patients accounted for in each group. Statistical differences in the survival curves were estimated using the Cox proportional hazards regression model according to the corresponding population table.
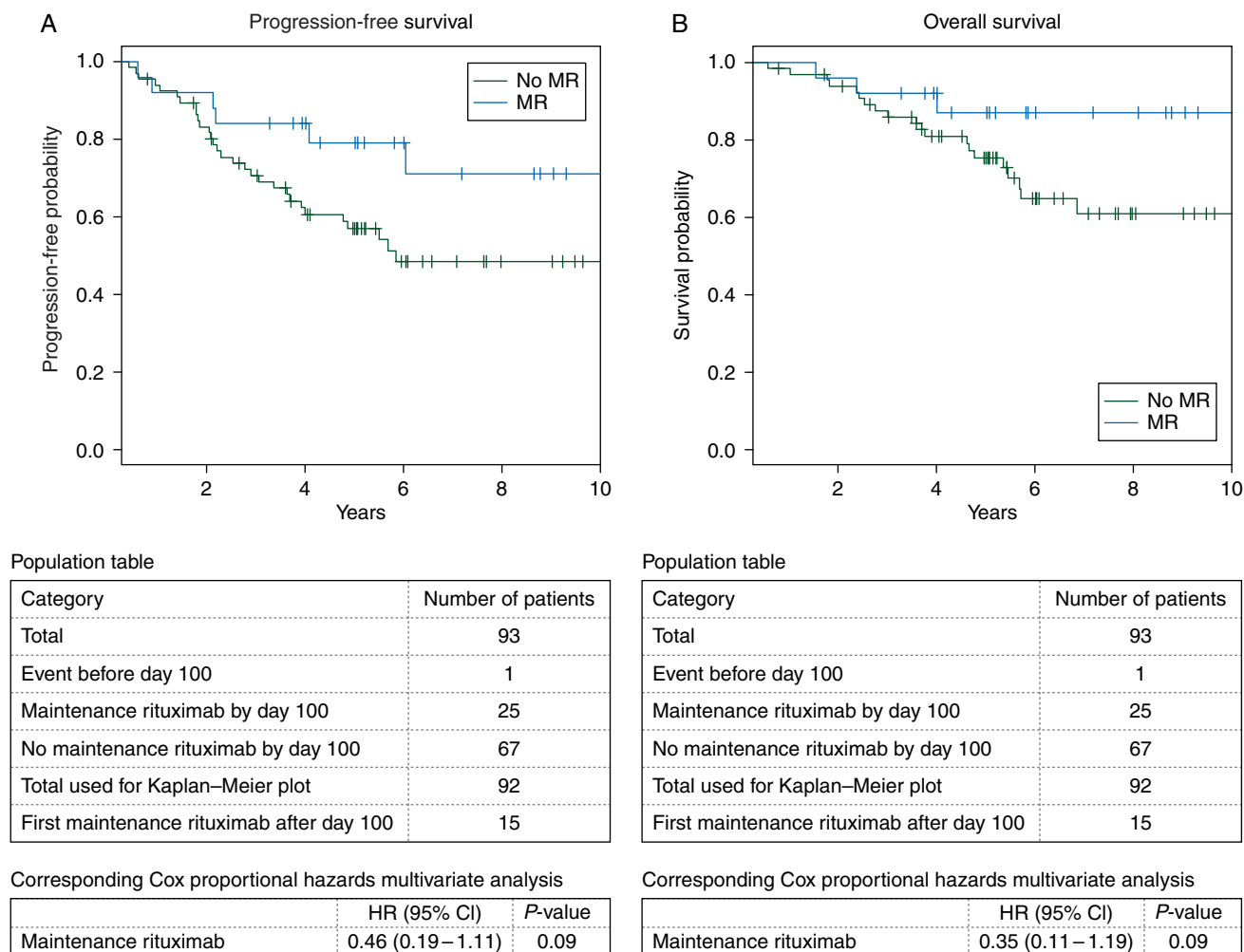
Figure 2. Kaplan–Meier plots using landmark of day 100 after autologous stem cell transplant (ASCT) depict the effect of MR on PFS (A) and OS (B) in the subgroup of patients who underwent ASCT in first complete remission or first partial remission. The population tables describe the number of patients accounted for in each group. Statistical differences in the survival curves were estimated using the Cox proportional hazards regression model according to the corresponding population table.

et al. that reported in a multivariate analysis of a cohort of 72 patients with MCL, 22 of whom received MR after ASCT, PFS was improved (HR 0.23; CI 0.06–0.80, $P = 0.02$) but OS was unchanged (HR 0.61; CI 0.14–2.65, $P = 0.51$) [11]. Le Gouill et al. recently presented interim analysis from the LyMa study (NCT00921414) designed to assess the impact of 3 years of MR after ASCT in patients with MCL and showed a statistically significant improvement in 2-year event-free survival (EFS) (93.2% with MR; CI 68.9%–96.6% versus 81.5% with no MR; CI 72.7%–87.7%, $P = 0.015$) but no effect, to date, on OS (2-year OS 93.4% with MR; CI 86.6–96.9 versus 93.9% with no MR; CI 86.7–97.3) [12]. Further maturation of these data is therefore awaited.

The mechanism for MR's efficacy in this population remains to be elucidated. The lack of interaction between MR effect and disease status at transplant ($P = 0.26$ for PFS and 0.92 for OS) argues against conversion to CR as the driving etiology, though minimal residual disease was not taken into account in this analysis. Alternatively, MR may postpone clinical disease relapse in those patients in whom molecular relapse has occurred [21]. MR after ASCT was associated with a twofold increased risk of severe

neutropenia (34% from 18%), a well-described phenomenon with, to-date, a poorly understood pathogenesis [22, 23]. Previously, a wide range (3.6%–54%) of severe neutropenia has been reported from studies investigating MR after ASCT in B-NHL [17–19], though our data are the first to quantify this toxicity compared with patients not receiving MR to account for underlying marrow damage from prior cytotoxic therapy. Reassuringly, the rates of NRM in the MR and no-MR groups were similar, suggesting that the increased incidence of neutropenia could be effectively managed and should not preclude the use of MR for this population, though it does mandate close clinical and laboratory follow-up and adds to the complexity and cost of this strategy. It is also likely that the prolonged B-cell depletion from this approach will delay successful immunization of patients after ASCT [24].

Despite the noted observations of this study, the retrospective, non-randomized design must be acknowledged before immediately applying this strategy to all MCL patients completing ASCT. MR was administered in a variety of dosing schedules and times after ASCT, adding to the heterogeneity of the findings but, arguably, also enhancing the applicability of these data to general

practice. Our data encompassed a wide span of time during which additional effective therapies in MCL were introduced and may have improved OS in patients with progression of disease after ASCT, though analyses investigating the impact of MR did show that the improvement in OS appears to be primarily consequent to delayed progression of disease. Though the multivariate adjustment accounted for some of the variation in characteristics between the two populations, the number of PFS and OS events did restrict the input of potential confounders into the models. As such, these data should primarily be used to set the stage for confirmation of benefit of MR after ASCT in MCL via prospective randomized trials, with maturation of the data from the aforementioned LyMa trial anticipated. In the meantime, this study adds to the growing body of evidence in support of using MR in MCL and is the first to suggest a survival advantage for its use after ASCT.

disclosure

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