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Deferred treatment is a safe and viable option for select patients with mantle cell lymphoma.

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Abstract

Prospective identification of candidates for deferred therapy is not standardized and many patients receive immediate therapy regardless of risk. We conducted a retrospective, multi-center cohort analysis of MCL patients with comprehensive clinical data to examine the use and safety of deferred therapy for newly diagnosed patients. Previously untreated patients 18 years-old with MCL diagnosed in 1993–2015 at five academic sites were included. Of 395 patients, 72 (18%) received deferred therapy (defined as receipt of first treatment > 90 days following initial diagnosis). Patients receiving deferred therapy were more likely to have an ECOG performance status of 0 (67% vs 44% $p=0.001$), have no B symptoms (83% vs 65% $p=0.003$) and have normal LDH levels at diagnosis (87% vs 55% $p<0.001$). In multivariable analysis, deferred therapy was not associated with a significant difference in OS (HR 0.64: 95% CI 0.22–1.84, $p=0.407$).

Keywords

mantle cell lymphoma; deferred therapy; non-Hodgkin's lymphoma

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JBC designed the study. OC, JJM, KAB, NG, SM, SIP, MG, AD, NE, TSF, and MH collected data and participated in quality control. OC, JMS and JBC conducted data analysis and interpreted the data. OC and JBC wrote the first version of the manuscript. JMS, JJM, KAB, NG, SM, SIP, MG, AD, NE, TSF, MH and CRF analyzed the data and substantially edited the manuscript. All authors reviewed and approved the final manuscript. The authors have declared no conflicts of interest.

Introduction

Despite the fact that mantle cell lymphoma (MCL) can have a heterogeneous clinical presentation ranging from indolent to very aggressive disease, the majority of patients are treated at the time of diagnosis regardless of initial presentation. Currently available prognostic markers in MCL, including the MCL International Prognostic Index (MIPI), Ki-67 proliferative index, cytogenetic assessments, IGVH mutation status, and SOX11 expression, assist with identification of high- and low- risk patients.[1–3] However, these prognostic tools are not frequently used in clinical practice to decide the timing of the initiation of first line therapy (immediate vs. deferred) for newly diagnosed patients.

Deferred therapy (i.e., a watchful waiting approach to newly diagnosed patients) has been evaluated in MCL in several prior reports. Martin et al. evaluated the role of deferred therapy in 97 newly diagnosed MCL patients in a single-center retrospective study.[4] Thirty-one patients delayed initial therapy for > 90 days with a median OS not reached among those deferred patients during the follow-up period. Abrisqueta et al. presented the British Columbia experience (in abstract form only) with a series of 439 patients with MCL in which 17% were observed > 3 months.[5] The seventy-five patients in this deferred group were more likely to have an ECOG performance status ≤ 1 , Ki-67 < 30%, normal LDH levels, and absence of B-symptoms, and these patients experienced a significantly longer median OS compared to the immediately-treated group (66 vs 50 months, $p=0.024$).

Our group recently published a national cohort analysis of 8,209 MCL patients captured in the National Cancer Data Base (NCDB) in which 501 patients received deferred therapy.[6] Features associated with deferred therapy included early stage disease, primary non-nodal disease, lack of B-symptoms, treatment at an academic/teaching center and residence in the Northeastern United States ($p<0.0001$).[6] Median OS was improved among deferred patients in a multivariable model (HR 0.79: 95% CI 0.67–0.93, $p=0.005$), and additional factors associated with improved OS included age ≥ 60 years, early stage disease, lack of B-symptoms and lack of co-morbidities ($p < 0.0001$). Among deferred patients, male gender ($p=0.046$), age ≥ 60 years ($p=0.0002$) and lack of comorbidities ($p < 0.0001$) were associated with improved OS.[6] As the NCDB does not capture patient-specific prognostic markers including laboratory values, performance status, and pathologic assessments, conclusions about patient-specific predictors of OS among deferred and non-deferred patients were limited. In addition, data regarding relapse are not available through NCDB, and progression-free survival (PFS) was therefore not analyzed. As a result, we conducted a multicenter analysis of MCL patients with comprehensive clinical and pathologic data to ascertain the use of deferred therapy and better describe its role in newly diagnosed MCL.

Patients and Methods

Patient Selection

Previously untreated patients ≥ 18 years old with MCL diagnosed between 1993–2015 and evaluated at one of five academic sites were included. Confirmation of the diagnosis of MCL was completed at each site at the time of patient evaluation and treatment. Based on the NCDB analysis and the Cornell experience, patients who initiated therapy > 90 days from

the time of diagnosis were considered to have received deferred therapy, while patients treated sooner than that time period were considered to have received immediate therapy.[4, 6] This retrospective chart review was approved by the Institutional Review Board at each participating site with waiver of informed consent.

Statistical Considerations

We evaluated demographic, clinical, laboratory and pathologic variables of interest for all patients and assessed their association with receipt of deferred therapy using ANOVA for numerical covariates and chi-square for categorical covariates. When available, MIPI was calculated for each patient, and the Ki-67 at diagnosis was assessed for each patient, using a cutoff of 30% to distinguish patients with high- vs low- Ki-67.[7] Complex karyotype (CK), defined as having > 3 unrelated chromosomal abnormalities detected by conventional cytogenetics, was also accessed.

We then evaluated the impact of these variables and the use of deferred therapy on PFS and OS using log-rank tests, as well as univariate and multivariable Cox proportional hazards models. For the primary analyses, PFS was calculated from the date of diagnosis to the date of first relapse/progression after initial treatment, death from any cause, or last follow-up. Progression of disease, leading to initiation of first line therapy in the deferred group was not considered an event of PFS. OS was calculated from the date of diagnosis to the date of death or last follow-up. Those lost to follow-up were censored at the time of last contact. However, we also performed a secondary, exploratory analysis of PFS from the date of first line therapy initiation to explore the impact of any potential bias related to the fact that all patients in the deferred group had to remain progression-free for at least 90 days. We evaluated the impact of each variable on PFS and OS in the subset of patients who received deferred therapy using a similar approach. PFS and OS were estimated using the Kaplan-Meier method. The proportional hazards assumption was checked by including the product of the log survival time and each covariate for each model, and assessing the statistical significance of that product. If the proportional hazards assumption was violated, hazard ratios were estimated both prior to and following the time point at which the survival curves crossed. Variables considered for the PFS multivariable analysis included B symptoms, ASCT, splenomegaly, CK, regimen, MIPI, and Ann Arbor stage. Variables considered for the OS multivariable analysis included the above variables, except stage. All patients who died and had available data for deferred therapy, B symptoms, ASCT, splenomegaly, CK, regimen, and MIPI were Stage 4. Due to the much smaller sample sizes, multivariable analyses for just deferred therapy patients included only MIPI, CK, and splenomegaly. For all analyses, statistical significance was determined at $p=0.05$. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Results:

Among all patients ($n=395$), the median age at diagnosis was 62 years (range 32–86 years), 72% were male, 96% were stage III/IV, and 32% presented with B symptoms (Table 1). Seventy-two patients (18%) received deferred therapy with a median time to treatment for

this group of 233 days (range 90 – 3651 days). Median time to treatment for the immediate group was 30 days (range 0 – 87 days).

Patients receiving deferred therapy were more likely to have an ECOG performance status of 0 (67% vs 44% $p=0.001$), lack B symptoms (83% vs 65% $p=0.003$) and have normal LDH at diagnosis (87% vs 55% $p<0.001$, Table 1). The deferred subgroup was also less likely to have bone marrow involvement at diagnosis (71% vs 84%, $p=0.013$) and to have splenomegaly (40% vs 57%, $p=0.013$).

Induction therapy was quite varied among all patients (Table 2), although patients receiving immediate therapy appeared to be more likely to receive aggressive therapy as nearly 1/3 of those patients received R-HyperCVAD. Additionally, deferred patients were less likely to receive an autologous hematopoietic cell transplant (AHCT) in first remission (26% vs 53%, $p<0.001$, Table 2).

Progression-free survival

The median PFS from the time of diagnosis was 3.8 years in the deferred group and 4.2 years for the immediately treated group ($p=0.409$, Figure 1a), and there remained no significant difference in PFS when evaluating PFS from the time of therapy initiation ($p=0.364$; Figure 1B). By univariate (UV) and multivariable (MV) analysis, complex karyotype (HR 3.21; 95% CI 1.49–6.92) was a statistically significant predictor of inferior PFS (Table 3). Induction regimen was also significantly associated with PFS in both models, where R-CHOP and R-Bendamustine appeared to have worse PFS compared to more aggressive regimens. As the deferred therapy variable violated the proportional hazards assumption in the MV model for PFS, we evaluated its impact on PFS both before and after the point where the curves cross (i.e., 4 years). In both analyses, there was no significant impact of deferred therapy on PFS (HR <4 years: 0.38, 95%CI: 0.14–1.01, $p=0.051$; HR > 4 years: 1.19, 95%CI: 0.16–9.02; $p=0.869$, See Table 3).

Overall Survival

Median OS for deferred patients was 11.8 years compared to 11.6 years for immediately treated patients ($p=0.352$) (Figure 2). Detailed in Table 3 are all the predictors of OS. Receipt of auto-transplant was associated with improved OS (HR 0.34; 95% CI 0.12–0.96) in both our UV and MV models (Table 3). Complex karyotype was associated with inferior OS (HR 3.56; 95% CI 1.57–8.11, Table 3). Deferred therapy was not associated with differences in OS (HR 0.64; 95% CI 0.22–1.84, Table 3).

Predictors of PFS and OS for Deferred Patients

UV and MV models for PFS and OS among deferred patients are presented in Supplementary Table 1 and Supplementary 2, respectively. Within the deferred subgroup, the MV models identified no variables significantly associated with PFS or OS.

Assessment of “Leukemic Phase” patients with MCL

The leukemic, non-nodal presentation of MCL has been associated with prolonged PFS and OS and an indolent disease course.[8] While we did not have available data to reliably

identify patients presenting with the leukemic, non-nodal presentation of MCL, we attempted to estimate outcomes for this group by analyzing those patients with WBC > 25,000, splenomegaly and non-bulky adenopathy (i.e., <5cm). We made the decision to include splenomegaly in this criterion since these patients typically present with splenomegaly and no/minimal lymphadenopathy. In the univariate model, this “leukemic” group of patients was not associated with differences in PFS or OS and therefore was not included in our multivariable models.

Evaluation of Additional Time Points to Determine Deferred Therapy

To potentially identify a more clinically meaningful observation period, we evaluated the impact of deferred therapy using 1 year and 2 years as cutoffs. Using a landmark analysis (to remove substantial survivorship bias), we evaluated OS and PFS when deferred therapy was defined as a period > 1 year or > 2 years. These additional analyses demonstrated no statistically significant difference in either OS or PFS between the immediately-treated and deferred therapy groups at either time points. In addition, we conducted a descriptive analysis of “ultra-deferred” patients who deferred therapy for greater than two years. Among these 14 cases, 100% of patients presented with normal LDH levels at diagnosis, 85% lacked bulky adenopathy (LN > 5cm), and 80% lacked a complex karyotype. In addition, ¾ of patients presented with an ECOG PS 1, 85% lacked B-symptoms and 69% lacked splenomegaly. Among this small subgroup, the median time to initiation of treatment was 3.2 years (range 2.1–10.0 years), and the median OS was 5.2 years from diagnosis and 3.0 years from the time of initial therapy.

Discussion:

Consistent with prior series, our multi-center cohort analysis suggests that a subset of MCL patients often characterized by indolent disease can be safely observed off therapy without a significant decrease in OS. Although most of the deferred patients ultimately initiated therapy within a year of diagnosis, many patients were able to defer therapy for > 1 year and 14 patients deferred therapy for > 2 years. This occurred without a decrease in OS, and it is possible that some of the other deferred therapy patients could have potentially waited longer to initiate therapy. As a result, there is likely a subgroup of patients with MCL who should be observed without treatment similar to our approach to chronic lymphocytic leukemia and indolent NHL.

Together, previous and current findings suggest that normal LDH levels, lower ECOG PS and lack of B-symptoms consistently predict the use of deferred therapy at diagnosis. MIPI risk group did not predict selection of deferred therapy. Also, although leukemic, non-nodal presentation of MCL has typically been associated with improved outcomes,[9–12] elevated WBC/splenomegaly/non-bulky adenopathy was not associated with differences in PFS or OS in our univariate models. However, we recognize that this construct was developed retrospectively and may not accurately identify patients with the true leukemic, non-nodal presentation. Due to the retrospective nature of our project, many in our cohort did not have an available baseline Ki-67 proliferative index (available for 156/395 patients only) and SOX11 expression was not available for included patients. In addition, patients were not

reliably assessed for the presence of a blastoid variant at the time of diagnosis and thus these data are not included.

Among deferred patients, Abrisqueta et al. and others have reported non-nodal presentation as the single significant factor associated with improved OS.[5, 8] The NCDB analysis further identified male sex, young age and a lack of co-morbidities as additional factors on univariate analysis. In our cohort, by both UV and MV analysis, deferred patients with a complex karyotype (CK) have an inferior prognosis compared to deferred patients without a CK. However, among the patients with a CK, the median PFS was improved for those who deferred therapy ($p=0.047$). Therefore, this raised the question of whether low-intensity chemotherapy could potentially induce chemo-resistance more easily in cases with more genetic instability (i.e. CK) as the CR rate is much lower for R-CHOP or B-R. Upon further analysis, among deferred patients with CK, 55% of patients received low-intensity immunochemotherapy (R-Bendamustine or R-CHOP) and 18% received dose-intensive therapy/high-dose therapy (DIT/HDT) in the form of R-HCVAD or R-M-CHOP. The rest received some other chemotherapy regimen. Unfortunately, since only 12 patients were deferred and CK, an assessment of survival based on treatment received was not possible. Together, this suggests that a CK alone should not be considered as a reason to initiate immediate therapy.

It is evident from this work that MCL comprises a broad spectrum of clinical behavior, suggesting that the underlying biology may be different depending on the clinical presentation. Comprehensive knowledge of each patient's mutational landscape, in addition to their laboratory values and histopathology, may aid in the identification of good candidates for deferred therapy. In fact, the current version of the NCCN guidelines [13] currently includes SOX11 status as a marker of indolent disease that can be considered when deciding about initiation of therapy and several groups have already identified candidate genomic abnormalities associated with inferior outcomes. We expect that with the advent of cost-effective CLIA-certified next-generation sequencing technologies, genomic assessments will be more readily accessible to patients and thus available for research purposes. The fact that deferring therapy does not adversely affect outcomes suggests that clinicians are often appropriately selecting patients for deferred therapy although an objective standard would be preferable, similar to what has been developed for indolent NHL.

We do recognize the limitations of this retrospective work. For example, given that we did not conduct a planned prospective study, but rather, an observational one, it is difficult to assess the superiority of deferred vs. immediate therapy (or vice versa). However, our data suggest that patients who are clinically chosen to be candidates for deferred treatment do not appear to have an adverse outcome due to waiting to initiate therapy. Many patients were initiated < 1 year after diagnosis, suggesting a limited clinical benefit of deferred therapy for those patients. However, since we don't know the specifics for why therapy was initiated in most patients, it is also possible that many of these patients could be deferred for even longer. Therefore, the fact that we found no clinical detriment to deferring therapy should provide support for physicians who are considering this approach in patients with indolent behaving disease and/or who are asymptomatic and to consider close observation as long as patients are not progressing or developing symptoms.

In addition, as with any retrospective project conducted at academic medical centers, selection bias likely contributed to our findings in this study. Our patient population included patients who likely had the resources to travel and were well enough to get another opinion regarding the management of their MCL as many of the patients did not have their initial diagnostic workup at the center. Although we did not consistently record which or how many patients were treated on study (i.e. clinical trial), it is safe to assume that the percentage is likely higher than in the general population. However, the fact that patients who were too sick to travel and/or had to start therapy immediately before seeking a second opinion were not included in this analysis likely strengthens our findings as those patients would have probably had an inferior outcome and may have negatively impacted the survival of the immediate therapy group.

Similarly, we did not have access to data regarding the presence or absence of del(17p) or *TP53* mutation status for patients in this series. Based on recent publications by the Nordic and European MCL groups indicating high risk disease associated with these abnormalities, [14, 15] we would recommend that patients be screened for these abnormalities at the time of diagnosis. However, the impact of a *TP53* mutation in a patient with otherwise indolent-behaving disease remains unclear.

We also recognize that the clinical decision to defer therapy was made by clinicians at the time of treatment and that the subsequent treatment utilized was heterogeneous. Our best attempt to precisely identify these criteria was to retrospectively identify factors associated with deferred vs. immediate therapy after these two treatment groups were defined using Martin et al.'s >90 day cut-off. Despite these limitations, we present a large cohort of patients treated for MCL at 5 centers throughout the United States which provides an opportunity to evaluate practice patterns at multiple centers. Based on our findings, those patients with an indolent presentation and limited symptoms can likely safely defer therapy until symptomatic progression. Continued efforts to develop molecular tools to reliably identify high-risk newly diagnosed MCL patients will hopefully soon allow for rational risk-adapted treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Progression-free survival from date of diagnosis – by treatment group. (b) Progression-free survival from date of first treatment – by treatment group.

Figure 2.
Overall survival – by treatment group.

Table 1.

Characteristics of Patient Groups

		Overall Group (N=395)	Immediate Group (N=323)	Deferred Group (N=72)	
Characteristic	No. (%)	No. (%)	No. (%)	p-value	
Median age, years	62	62	63	0.04	
Male gender	284 (72)	239 (74)	45 (63)	0.05	
ECOG PS				0.001	
0	146 (49)	107 (44)	39 (67)		
1	132 (44)	119 (49)	13 (22)		
2/3/4	23 (7)	17 (7)	6 (10)		
Ann Arbor Stage				0.048	
I	3 (1)	1 (0.32)	2 (3)		
II	14 (4)	11 (3.5)	3 (4)		
III	32 (8)	23 (7)	9 (13)		
IV	333 (87)	279 (89)	54 (79)		
B symptoms	117 (32)	106 (35)	11 (17)	0.003	
Elevated LDH	110 (39)	103 (45)	7 (13)	<0.001	
Bone Marrow +	299 (82)	252 (84)	47 (71)	0.013	
Splenomegaly	180 (54)	154 (57)	26 (40)	0.013	
WBC					
<10	211 (65)	176 (66)	35 (59)		
10–25	69 (21)	51 (19)	18 (31)		
25+	46 (14)	40 (15)	6 (10)	0.129	
Confirmed GI Involvement	61 (24)	51 (25)	10 (20)	0.479	
LN > 5cm	73 (22)	62 (24)	11 (17)	0.248	
LN > 10cm	15 (5)	12 (5)	3 (5)	0.99	
Ki-67 >30%*	53 (49)*	47 (51)	6 (38)	0.335	
	Missing - 286				
Complex Karyotype	51 (20)	39 (19)	12 (24)	0.47	
	Missing - 144				
MIPI risk group**				0.422	
low	68 (33)	57 (35)	11 (25)		
intermediate	80 (38)	61 (37)	19 (42)		
high	61 (29)	46 (28)	15 (33)		
	Missing - 186				
Median WBC	8	8	8.3	0.594	
Year of Diagnosis				0.856	
2006 & earlier	94 (24)	74 (23)	20 (28)		
2007–2009	81 (21)	67 (21)	14 (19)		
2010–2012	115 (29)	95 (29)	20 (28)		
2013–2015	105 (26)	87 (27)	18 (25)		

Characteristic	Overall Group (N=395)	Immediate Group (N=323)	Deferred Group (N=72)	p-value
	No. (%)	No. (%)	No. (%)	
Leuk25	30 (11)	26 (12)	4 (8)	0.377
	Missing - 121			
Leuk10	51 (19)	43 (19)	8 (15)	0.464
	Missing - 121			

Abbreviations:

ECOG PS, Eastern Cooperative Oncology Group performance status

LDH, lactate dehydrogenase

WBC, white blood cell count

LN, lymph node

Complex Karyotype: defined as the presence of 3 chromosomal abnormalities

MIPI: Mantle Cell International Prognostic Index

* Ki-67 proliferation index available for only 109 of 395 total patients

** MIPI available for only 209 of 395 total patients

Leuk25: WBC > 25,000, splenomegaly and non-bulky adenopathy (i.e., <5cm)

Leuk10: WBC > 10,000, splenomegaly and non-bulky adenopathy (i.e., <5cm)

Table 2.

Treatment Characteristics

Characteristic	Immediate Group (N=323)	Deferred Group (N=72)	p-value
	No. (%)	No. (%)	
Median time to treatment	30 days (0–87)	233 days (90–3651)	<0.001
Induction Regimen			<0.001
R-CHOP	52 (16)	7 (12.28)	
R-HyperCVAD	109 (34)	10 (17.54)	
R-Bendamustine	40 (12)	9 (15.79)	
R-M-CHOP	45 (11.25)	3 (5.26)	
R-CHOP/R-DHAP	16 (5)	1 (1.75)	
BR-Bortezomib	8 (2.5)	0 (0)	
R-Cladribine	15 (4.69)	12 (21.05)	
Other *	47 (14.69)	15 (26.32)	
Nordic Regimen	3 (0.94)	0 (0)	
Auto-transplant in 1st remission	153 (53)	14 (26)	<0.001

* "Other" induction regimens included R-Revlimid, R-BAC, R-CVP, Fludarabine-Flavopiridol-Rituxan and Rituxan monotherapy, among others.

Table 3.

Predictors of PFS and OS

Covariate	Level	N*	PFS		OS	
			UV (95% CI)	MV (95% CI)	UV (95% CI)	MV (95% CI)
Deferred treatment	Yes	72			0.77 (0.44–1.34)	0.64 (0.22–1.84)
	No	323			-	-
Deferred therapy (Less than 4 years)	Yes		0.76 (0.50–1.18)	0.38 (0.14–1.01)		
	No					
Deferred therapy (Greater than 4 years)	Yes		1.33 (0.60–2.97)	1.19 (0.16–9.02)		
	No					
Gender	Female	111	0.88 (0.63–1.24)		1.00 (0.63–1.60)	
	Male	284	-		-	
Ethnicity	White/Hispanic	273	0.59 (0.33–1.06)		0.48 (0.23–1.03)	
	Black	21	0.34 (0.13–0.91)		0.43 (0.11–1.63)	
	Others/Unknown	26	-		-	
ECOG	0	146	0.42 (0.22–0.78)		0.21 (0.10–0.44)	
	1	132	0.64 (0.35–1.20)		0.35 (0.17–0.73)	
	2/3/4	23	-		-	
Ann Arbor Stage	I/II	17	0.51 (0.24–1.09)	3.49 (0.36–33.37)	0.62 (0.23–1.70)	
	III	32	0.64 (0.37–1.11)	0.34 (0.07–1.66)	0.27 (0.09–0.85)	
	IV	333	-	-	-	
B symptoms	Yes	117	1.52 (1.11–2.09)	1.11 (0.54–2.32)	2.16 (1.39–3.34)	1.69 (0.78–3.65)
	No	249	-		-	-
LDH	Elevated	110	2.29 (1.58–3.31)		2.73 (1.65–4.53)	
	Normal	176	-		-	
WBC (cat - 3 levels)	25+	46	2.05 (1.31–3.20)		2.16 (1.20–3.88)	
	10–25	69	0.94 (0.62–1.44)		1.25 (0.71–2.19)	
	<10	211	-		-	
GI involvement	Yes	61	1.14 (0.70–1.87)		1.10 (0.50–2.43)	
	No	195	-		-	
BM involvement	Yes	299	1.74 (1.14–2.64)		2.07 (1.09–3.93)	
	No	66	-		-	
Splenomegaly	Yes	180	1.71 (1.22–2.39)	1.72 (0.86–3.45)	2.05 (1.25–3.37)	2.04 (0.94–4.45)
	No	155	-		-	-
LN > 5cm	Yes	73	1.73 (1.21–2.46)		1.59 (0.96–2.63)	
	No	255	-		-	
LN > 10cm	Yes	15	1.52 (0.77–2.99)		1.18 (0.43–3.25)	
	No	312	-		-	
Ki-67	Unknown	239	1.30 (0.84–2.02)		1.56 (0.80–3.04)	
	>30%	77	2.27 (1.36–3.78)		1.97 (0.90–4.30)	
	<=30%	79	-		-	
Complex Karyotype	Yes	50	2.81 (1.86–4.26)	3.21 (1.49–6.92)	3.52 (2.05–6.04)	3.56 (1.57–8.11)

Covariate	Level	N*	PFS		OS	
			UV (95% CI)	MV (95% CI)	UV (95% CI)	MV (95% CI)
Induction regimen	No	201	-		-	-
	R-CHOP	60	3.28 (2.08–5.17)	10.74 (3.62–31.88)	1.94 (1.00–3.76)	1.81 (0.59–5.55)
	R-HCVAD	119	1.39 (0.89–2.17)	3.44 (1.09–10.90)	1.46 (0.77–2.75)	2.04 (0.59–7.07)
	R-Bendamustine	51	2.85 (1.65–4.91)	12.78 (3.73–43.78)	2.16 (0.93–5.03)	2.63 (0.68–10.22)
	RMCHOP	48	0.99 (0.56–1.75)	1.89 (0.45–7.88)	1.50 (0.71–3.16)	2.79 (0.65–11.98)
Auto-transplant	Others	104	-	-	-	-
	Yes	167	0.44 (0.32–0.60)	0.47 (0.20–1.14)	0.58 (0.37–0.92)	0.34 (0.12–0.96)
MIPI risk group	No	177	-		-	-
	Low	68	0.59 (0.37–0.94)	1.39 (0.56–3.47)	0.77 (0.41–1.46)	1.56 (0.61–4.01)
	Intermediate	80	0.98 (0.66–1.45)	2.22 (0.94–5.22)	1.14 (0.64–2.03)	1.06 (0.43–2.58)
	High	61	1.34 (0.88–2.05)	-	1.73 (0.97–3.08)	0.53 (0.18–1.59)
	Unknown	186	-		-	-
Post-induction rituximab	Yes	73	0.51 (0.32–0.79)		0.09 (0.02–0.37)	
	No	322	-		-	
Year of diagnosis	2006 and earlier	94	1.17 (0.70–1.97)		1.49 (0.63–3.51)	
	2007–2009	81	0.93 (0.54–1.60)		1.12 (0.46–2.73)	
	2010–2012	115	0.68 (0.39–1.17)		0.90 (0.37–2.22)	
	2013–2015	105	-		-	
Leuk25	Yes	30	1.91 (1.08–3.36)		1.55 (0.70–3.44)	
	No	244	-		-	
Leuk10	Yes	51	1.19 (0.74–1.90)		1.47 (0.79–2.74)	
	No	223	-		-	
Age at diagnosis		380	1.02 (1.00–1.03)		1.03 (1.00–1.05)	
WBC		326	1.01 (1.00–1.01)		1.01 (1.00–1.01)	

* Note that these sample sizes are only applicable to the univariate analysis.