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Retrospective analysis of bendamustine and rituximab use in indolent and mantle cell non-Hodgkin lymphoma based on initial starting dose

David A. Bond^a, Ying Huang^b, Amy S. Ruppert^b, Alison R. Walker^b, Emily K. Dotson^c, Julianna Roddy^c, Kristie A. Blum^b, and Beth A. Christian^b

^aDepartment of Internal Medicine, The Ohio State University, Columbus, OH, USA

^bDivision of Hematology, The Ohio State University, Columbus, OH, USA

^cDepartment of Pharmacy, The Ohio State University, Columbus, OH, USA

Abstract

The initial dose of bendamustine, an alkylating agent used in treating indolent lymphoma (iNHL) and mantle cell lymphoma, is variable in clinical practice. 134 patients treated with bendamustine and rituximab were evaluated for starting dosage, patient characteristics, toxicities, and clinical outcome. The starting dosage ranged from 50 to 90 mg/m². Lower starting dosage (<90 mg/m²) was associated with relapsed disease, increased age and worse performance status (PS), histologic subtype other than follicular lymphoma, baseline renal impairment, and cytopenias. No significant difference was observed in toxicities between patients treated with 90 mg/m² compared with lower doses. The starting dose of 90 mg/m² was associated with a higher complete response rate (56% vs. 29%) and longer progression free survival (PFS) (39.5 months vs. 19.7 months). However, in a multivariable model, the higher starting dose was not associated with longer PFS in those with similar age, histology, PS, and number of prior therapies.

Keywords

Bendamustine; lymphoma and Hodgkin disease; immunotherapeutic approaches

Introduction

Bendamustine (Treanda[®]; Cephalon, Inc., Frazer, PA) is a bifunctional alkylating agent first synthesized in the 1960's and employed for decades as monotherapy for chronic lymphocytic leukemia, non-Hodgkin lymphoma (NHL), multiple myeloma, and breast cancer.[1,2] Studies in the United States first used the drug for treatment of NHL as a single agent in the setting of refractory disease. In a phase II study, 76 patients with rituximab-refractory, indolent NHL (iNHL) treated with single agent bendamustine at a dose of 120

CONTACT Beth Christian, Beth.christian@osumc.edu, 320 West 10th Avenue, A348 Starling Loving Hall, Columbus, OH 43210, USA.

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mg/m² on days 1 and 2 of a 28-day cycle were shown to have an overall response rate (ORR) of 77%.[3] A separate study confirmed these results with 100 patients with rituximab refractory iNHL with single agent bendamustine demonstrating an ORR of 75% with an acceptable toxicity profile.[4] On the basis of these trials, bendamustine received FDA approval on 31 October 2008 for the treatment of rituximab-refractory iNHL at a recommended dose of 120 mg/m².

The use of the CD20 monoclonal antibody rituximab (Rituxan®; Genentech, Inc., South San Francisco, CA) in the treatment of NHL has resulted in significant improvement in response and survival.[5] Combination therapy with rituximab and chemotherapy has become a common frontline therapy for iNHL and MCL.[6] A phase II study of 63 iNHL patients demonstrated the safety and activity of bendamustine dosed at 90 mg/m² plus rituximab as initial therapy.[7] In a subsequent phase III non-inferiority trial, patients with newly diagnosed iNHL and MCL were randomized to receive either RCHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) or rituximab plus bendamustine (R-bendamustine). Patients treated with R-bendamustine had less infectious and hematologic toxicity and were found to have a statistically significant increase in progression-free survival (PFS).[8] A second phase III study confirmed the non-inferiority of R-bendamustine when compared with RCHOP or RCVP and again demonstrated an acceptable toxicity profile.[9] Recent studies examining the safety and efficacy of combining additional agents with R-bendamustine for patients with relapsed iNHL and MCL have shown promising results which require validation in larger trials.[10–13].

The optimal starting dosage of bendamustine is subject to variability in clinical practice. The initial studies of single agent bendamustine used a dose of 120 mg/m², and phase III studies of chemoimmunotherapy with R-bendamustine used a dose of 90 mg/m². [3,4,8,9,14,15] A retrospective study of 940 patients with both NHL and CLL noted a mean dosage of bendamustine of 77.3 mg/m² in patients with a creatinine clearance (CrCl) <40 mg/mL versus 84.5 mg/m² in those with CrCl ≥ 40 mg/mL, suggesting renal function was a factor in dosing choice.[16] As bendamustine is explored in new combinations, the optimal starting dosage remains unclear, particularly since comorbidities, advanced age, multiple prior treatments, and other risk factors for toxicity in patients encountered in clinical practice may lead clinicians to utilize a lower starting dose. The aim of our study is to retrospectively evaluate patients treated with R-bendamustine for iNHL and MCL in order to describe the variability in initial dosing, determine the factors which influence the choice of initial starting dose, and compare toxicities and clinical outcome.

Materials and methods

Indolent NHL and MCL patients treated with R-bendamustine from 1 October 2008 to 1 January 2014 were identified using a pharmacy database. Data collected included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histologic subtype of iNHL, stage at diagnosis and treatment, baseline CrCl, number of prior therapies, prior stem cell transplant (SCT), starting dose of bendamustine, and presence of neutropenia or thrombocytopenia at onset of treatment. CrCl was calculated with the Modification of Diet in Renal Disease formula. Neutropenia was defined as absolute neutrophil count of less

than the institutional laboratory reference range of 1800 per microliter, and thrombocytopenia was defined as platelet count of less than the institutional reference range of 150,000 per microliter. Data from treatment including number of cycles, dose reduction or delay, grade 3 or 4 hematologic toxicity, infectious toxicities of any grade, number of transfusions, and use of granulocyte colony stimulation factor (G-CSF) during treatment were collected. Grade 3 or 4 hematologic toxicities were defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Dose intensity (DI) of bendamustine in $\text{mg}/\text{m}^2/\text{week}$ for up to 6 cycles of treatment was calculated as the average amount of bendamustine received by patient per week for each patient individually using the method proposed by Hryniuk and Goodyear.[17,18] Relative dose intensity (RDI) was calculated as the ratio of DI and standard dose intensity ($45 \text{ mg}/\text{m}^2/\text{week}$ corresponding to $90 \text{ mg}/\text{m}^2/\text{cycle}$). Additionally, charts were reviewed to determine if patients developed myelodysplastic syndrome (MDS), or therapy-associated acute myeloid leukemia (tAML) following treatment. Response, determined by NHL international response criteria and Waldenström's international working group response criteria,[19,20] time to progression, and time to death were recorded for each patient. ORR was defined as patients achieving either complete response (CR) or partial response (PR) for NHL excluding Waldenström's macroglobulinemia (WM) and as CR, very good partial response (VGPR), and PR in patients treated for WM. The institutional review board of Ohio State University approved the protocol according to the Declaration of Helsinki.

Baseline characteristics, toxicity, DI, RDI and response were compared between patients receiving a starting dose of bendamustine of $90 \text{ mg}/\text{m}^2$ and those receiving $<90 \text{ mg}/\text{m}^2$ using Fisher's exact tests or Wilcoxon rank sum tests. PFS was calculated from cycle one day one of bendamustine until progression or death, whichever occurred first, censoring patients at the date last known progression-free. Overall survival (OS) was calculated from cycle one day one of bendamustine until the date of death, censoring patients who were alive at last follow-up. PFS and OS were described using the Kaplan Meier method and the log-rank test was used to compare the survival curves between groups. Logistic regression and proportional hazards (PH) model were used to model CR and PFS/OS respectively as a function of starting dose, adjusting for other significant and confounding covariates. Univariable models for each endpoint were first fit. Multivariable models were then built using $p < .05$ for forward selection. Variables considered included age, gender, histology, number of prior chemotherapies, ECOG PS, disease stage, baseline CrCl, pretreatment neutropenia and thrombocytopenia. All models included starting dose, regardless of statistical significance. The proportional hazard assumption was checked for each covariate included in the final PH model. ECOG PS as a continuous variable did not meet the PH assumption, so it entered the PH models as a dichotomized variable. For OS, the number of events was limited and the final model only included the two most significant covariates. All tests were two-sided, statistical significance was set at $\alpha = .05$, and SAS 9.3 (Cary, NC) was used for all statistical analyses.

Results

A total of 134 patients treated with R-bendamustine meeting the inclusion criteria were identified. Eighty-four (63%) patients received bendamustine at a starting dose level of 90

mg/m² and 50 (37%) patients received less than 90 mg/m². Within the lower starting dose cohort, the dose was 75 mg/m² and 72 mg/m² in one patient for each respective dose, 70 mg/m² in 11 patients, 60 mg/m² in 35 patients, and 50 mg/m² in two patients.

Baseline characteristics for all patients and according to initial bendamustine dose are summarized in Table 1. The histology of iNHL was predominantly FL (51%). The majority of patients had stage IV disease (77%) and had received at least 1 prior therapy (60%). Eleven (8%) patients had prior autologous stem cell transplant; one of these eleven patients also had a prior allogeneic stem cell transplant. At the initiation of therapy 46 (34%) patients were thrombocytopenic, and 10 (7%) patients were neutropenic. Fifty-four (40%) patients received G-CSF during treatment.

A significantly higher proportion of patients treated with a starting dose of 90 mg/m² had follicular lymphoma compared with patients treated with lower starting dose (62% v 34%). Increasing age, higher ECOG performance status, higher number of prior therapies and lower baseline CrCl were significantly associated with a lower initial starting dosage. Patients treated with a lower starting dose also had higher incidence of pretreatment thrombocytopenia and neutropenia.

Toxicity and treatment intensity is summarized in Table 2. Grade 3 or 4 hematologic toxicities were observed in 38 of 134 (28%) patients treated with R-bendamustine, 25% with a starting dose of 90 mg/m² versus 34% with initial bendamustine dose <90 mg/m². Infectious toxicity occurred in 27 patients (20%), at an equal frequency in patients receiving 90 mg/m² bendamustine versus <90 mg/m². Transfusions were required in 20 patients (15%), 11% with a starting dose of 90 mg/m² versus 22% with initial bendamustine dose <90 mg/m². Dose reductions, delays, or cessation of bendamustine therapy occurred for 54 patients (40%). The most frequent reasons for delay or dose reduction were myelosuppression ($n = 21$), infection ($n = 8$), and rash ($n = 4$). Therapy was stopped due to disease progression in 8 patients. Dose reduction or delay occurred in a similar percentage of patients treated with a starting dose of bendamustine of 90 mg/m² of bendamustine compared with those treated with a starting dose less than 90 mg/m² (41% vs. 40%). Median RDI was 1 (range: 0.3–1) in patients with a starting dose of 90 mg/m², indicating that most patients who started at that dose received the standard dosing of 90 mg/m² throughout treatment. In the patients who began at starting dose less than 90 mg/m², the median RDI was 0.7 (range: 0.5–1). Thus, the starting dose was significantly associated with RDI ($p < .0001$) and reflected the overall dose intensity of bendamustine.

MDS or tAML was observed in 2 patients following treatment with R-bendamustine at starting doses of bendamustine of 70 and 60 mg/m² respectively. Both of these patients had prior alkylating chemotherapy. Seven patients went on to receive allogeneic SCT and two patients went on to autologous SCT with no difficulty in collecting stem cells noted.

Following treatment with R-bendamustine, 61 (46%) patients achieved CR, 56 (42%) patients achieved PR/ VGPR, 4 (3%) patients had stable disease (SD), 11 (8%) patients had progressive disease (PD), and 1 patient had a hypersensitivity reaction to bendamustine and switched to alternate therapy. Of 13 patients with WM or LPL, 4 achieved VGPR, 8

achieved PR, and 1 patient was lost to follow-up and response is unknown. Responses are summarized in Table 3. The ORR for the entire cohort was 89% (95%CI: 82–94%), and no statistically significant difference was observed in the ORR between the two starting dose groups ($p = .78$). The CR rate for all patients was 46% (95%CI: 38–55%), and was significantly higher in the starting dose of 90 mg/m² group compared with those treated with lower starting dose (56% v 29%, odds ratio (OR) = 3.1, 95%CI: 1.5–6.6; $p = .004$).

Several baseline characteristics were also significantly associated with failure to achieve CR including male gender, higher PS, and lower CrCl. Since higher PS and lower CrCl were also correlated with lower starting dose, the association between bendamustine starting dosage of 90 mg/m² and higher rate of CR was partially accounted for by these confounding variables after they were adjusted for in the multivariable model (OR 1.8, 95%CI: 0.8–4.5; $p = .18$), as reported in Table 4.

With a median follow-up of 25 months (range 0.1–67 months), 99 patients were alive at last follow-up and 35 patients have died. The median PFS and OS for all patients was 25 months (95%CI: 18–not reached) and 59 months (95%CI: 59–not reached), respectively. For those treated with a starting dose of 90 mg/m² the median PFS was 39.5 months (95%CI: 18.3–not reached) versus 19.7 months (95%CI: 13.6–30.5 months) for patients with a starting dose less than 90 mg/m² ($p = .06$, Figure 1(a)). The median OS has not been reached in 90 mg/m² group, and it was 39.2 months (95%CI: 22.8–58.9 months) in the lower starting dose group ($p = .11$, Figure 2(a)).

Baseline characteristics significantly associated with worse PFS included older age, higher PS, MCL, and more lines of prior therapy (Tables 5). These factors were also highly correlated with lower starting dose level. Once accounting for patients with similar age, MCL status, PS, and number of prior therapies, the risk of progression or death attributed to starting dose level was actually higher in those with a starting dose of 90 mg/m² versus <90 mg/m² (hazard ratio (HR) = 1.7, 95%CI: 0.9–3.2; $p = .09$). In the same manner, the risk of death was higher in 90 mg/m² starting dose group (HR = 1.1, 95%CI: 0.6–2.4; $p = .74$), after accounting for poor PS (>1) and MCL Table 6. The adjusted curves for PFS and OS according to starting dose and fixing values for all other variables in the model are illustrated in Figures 1(b) and 2(b).

Discussion

While starting dosages from 90 to 120 mg/m² were used in clinical trials of bendamustine as a single agent and in combination with rituximab for the treatment of NHL, the starting dose utilized in clinical practices is variable. The extent of this variability, reasons for utilizing a lower starting dose, and how this impacts toxicity and clinical outcome has not previously been well described. In our series of 134 patients treated with R-bendamustine for iNHL and MCL, 50 (37%) received a bendamustine starting dose of less than 90 mg/m². Of those who started at a dose less than 90 mg/m², 70% started at 60 mg/m², 22% starting at 70 mg/m² and a smaller percentage of patients started at dosages of 75, 72, and 50 mg/m². Choice of a lower starting dosage correlated with increased age and ECOG PS, decreased baseline CrCl, fewer prior therapies, and histologic subtypes other than FL. In addition, patients treated

with a lower starting dosage were more likely to have neutropenia and thrombocytopenia at initiation of treatment.

No significant difference was seen in toxicities in our study between patients treated with initial doses of bendamustine of 90 mg/m² compared with those treated with lower starting doses. Many of the characteristics associated with utilizing a lower starting dose such as greater number of prior therapies, PS of 2 or greater, pretreatment neutropenia and thrombocytopenia, and decreased CrCl are risk factors for myelosuppression and toxicity. Despite these risk factors, the incidence of grade 3 and 4 hematologic toxicity was not significantly different between groups (25% in the 90 mg/m² group vs. 34% in the less than 90 mg/m² group, 95%CI on the percent difference: -25% to 7%; $p = .32$), suggesting that the lower starting dose mitigated toxicity in the more frail patient population.

We compared starting dose of bendamustine with toxicity and clinical outcome, but this does not account for subsequent dose increases/decreases throughout the course of therapy. RDI, measured in mg/m²/week, accounts for the average dose delivered over all cycles as well as delays due to toxicity. In the patients analyzed, those receiving the standard bendamustine starting dose of 90 mg/m² on average received a significantly higher RDI throughout the course of treatment than those treated with an initial dose reduction, which indicates that starting dose mirrors the intensity of treatment.

Prospective studies of bendamustine and rituximab for the treatment of iNHL and MCL both in the relapsed and frontline setting have shown excellent response rates of 90% or greater. [7–9,15] The ORR in this series which included both treatment-naïve patients and patients with relapsed or refractory disease was 89% (95%CI: 82–94%), which is comparable to that of historical studies. There was no statistically significant difference in ORR between patients starting at a bendamustine dose of 90 mg/m² (ORR = 89%) versus lower than 90 mg/m² (ORR = 88%, 95%CI on the percent difference: -10% to 13%; $p = .78$).

CR rate was superior in patients receiving a higher starting dosage of bendamustine, but this difference was partially explained by confounding variables including gender, ECOG PS, and differences in baseline CrCl. In a recent prospective study, patients with relapsed or refractory WM were treated with bendamustine and rituximab with starting dosage of bendamustine determined at the discretion of the treating physician. In this study, similar to our series, there was no significant difference in toxicity, ORR, and duration of response between starting doses with 31% of patients receiving a starting dosage of bendamustine of 70 mg/m² and 6% treated with 50 mg/m². [21] A higher proportion of patients treated with a starting bendamustine dose of 90 mg/m² achieved CR, but the authors noted potential bias with a tendency for more frail patients to be treated with a lower starting dosage. [21]

In our study with a median patient age of 68 years, male gender was associated with lower odds of complete response (OR = .28, $p = .004$). This is consistent with recent literature suggesting that male gender is an adverse predictive factor for older adults with B cell lymphoma in the rituximab era. [22–25] Gender associated differences in the pharmacokinetics of rituximab has been postulated as a potential explanation for this disparity. [25] The mechanism for this gender-associated discrepancy in response and the

optimal dosing of rituximab in older males with B cell lymphoma remains an area of uncertainty which warrants further investigation.

Decreased CrCl was noted to be an independent negative predictor of complete response in this study. The metabolism of bendamustine appears to be primarily independent of renal excretion and rather via rapid hydrolysis.[26] In a previously mentioned retrospective study, patients with a CrCl of less than 40 mL/min had higher rates of thrombocytopenia and increased blood urea nitrogen, with similar rates of non-laboratory adverse events; clinical response to treatment was not reported.[16] Impaired renal function may correlate with other comorbid conditions conferring a worse prognosis and would not offer a pharmacokinetic advantage in terms of higher concentrations of active drug as the metabolism is primarily non-renal.

The median PFS observed in our series was 25 months (95%CI: 18-not reached), which is also similar to previous reports. The median PFS in patients treated with a starting dose of 90 mg/m² was longer than that for patients treated with a lower starting dose (39.5 months vs. 19.7 months). High-risk features significantly associated with worse PFS such as older age, MCL, and higher PS were also highly correlated with lower starting dose level, so even though PFS was lower in patients receiving lower dose, this is in part a reflection of the high risk features of patients in this group.

We acknowledge the limitations of this retrospective study including the potential for unidentified confounding variables or inadequate sample size to identify differences in toxicity or response as a function of starting dose. With the number of patients included in this study, there was sufficient power to detect only large differences in toxicity or response rates between groups (e.g. 35% vs 60% or a 25% difference). With these limitations in mind, this study did not demonstrate any significant difference in toxicities associated with choice of a lower starting dose of bendamustine. CR rate was higher and PFS longer for the group of patients receiving a starting dose of 90 mg/m². However, comparing patients with similar age, MCL status, PS, and number of prior therapies, lower starting dose did not adversely affect PFS. Our study highlights the variability in dosing of bendamustine in clinical practice, particularly in older adults, patients with higher ECOG performance status, and those with multiple prior lines of treatment.

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Figure 1.

Unadjusted (a) and adjusted (b) results for progression-free survival according to starting dose of bendamustine. The unadjusted comparison for starting dose is shown with the Kaplan–Meier curves and compared using the log-rank test. The adjusted comparison of starting dose is shown with fitted curves from the model for a typical patient with high-risk factors (e.g. age = 68 years, disease = MCL, performance status = 2/3, and number of prior therapies = 2).

Figure 2.

Unadjusted (a) and adjusted (b) results for overall survival according to starting dose of bendamustine. The unadjusted comparison for starting dose is shown with Kaplan-Meier curves and compared using the log-rank test. The adjusted comparison of starting dose is shown with fitted curves from the model for a typical patient with high-risk factors (e.g. disease = MCL, and performance status = 2/3).

Table 1Baseline patient characteristics by starting dose of 90 mg/m² vs. lower starting dose.

Baseline characteristic	Overall <i>n</i> = 134	Starting dose = 90 mg/m ² <i>n</i> = 84	Starting dose <90 mg/m ² <i>n</i> = 50	<i>p</i> -Value
Age, years				<.0001
Median	68	62	75	
Range	23–86	23–82	46–86	
Sex, no. (%)				.86
Male	76 (57)	47 (56)	29 (58)	
Female	58 (43)	37 (44)	21 (42)	
Histologic subtype, no. (%)				.008
FL	69 (51)	52 (62)	17 (34)	
MCL	30 (22)	15 (18)	15 (30)	
iNHL	35 (26)	17 (20)	18 (36)	
ECOG PS Group, no. (%)				.03
0	51 (41)	39 (48)	12 (28)	
1	58 (47)	36 (44)	22 (51)	
2/3	15 (12)	6 (7)	9 (21)	
Missing	10	3	7	
Stage of disease at time of bendamustine treatment, no. (%)				.15
I/II	9 (7)	8 (10)	1 (2)	
III/IV	113 (93)	70 (90)	43 (98)	
Missing	12	6	6	
Baseline Cr Cl (GFR), no. (%)				.01
40	13 (10)	3 (4)	10 (20)	
41–59	27 (20)	17 (20)	10 (20)	
60	93 (70)	63 (76)	30 (60)	
Missing	1	1	0	
Number of prior chemotherapy				.002
Median	1	0	2	
Range	0–7	0–7	0–7	
Previously treated, no. (%)				.001
No	54 (40)	43 (51)	11 (22)	
Yes	80 (60)	41 (49)	39 (78)	
Baseline neutropenia, no. (%)				.006
No	124 (93)	82 (98)	42 (84)	
Yes	10 (7)	2 (2)	8 (16)	
Baseline thrombocytopenia, no. (%)				.005
No	88 (66)	63 (75)	25 (50)	
Yes	46 (34)	21 (25)	25 (50)	

FL: follicular lymphoma; MCL: mantle cell lymphoma; no.: number; ECOG PS: Eastern Cooperative Oncology Group performance status; CrCl: creatinine clearance; iNHL – indolent NHL including lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia and marginal zone lymphoma.

Table 2Toxicity and treatment intensity by starting dose of 90 mg/m² vs. lower starting dose.

	Starting dose = 90 mg/m ² n = 84	Starting dose <90 mg/m ² n = 50	p-value
Toxicity, no. (%)			
Grade 3/4 hematologic toxicity	21 (25)	17 (34)	.32
Infectious toxicity	17 (20)	10 (20)	1.00
Transfusions	9 (11)	11 (22)	.09
Reduction/delay	34 (41)	20 (40)	1.00
Treatment intensity			
Dose intensity, mg/m ² /week			<.0001
Mean (SD)	41.5 (7.1)	31 (4.5)	
Median (range)	45 (13–45)	30 (21.1–45)	
Relative dose intensity			
Mean (SD)	0.9 (0.2)	0.7 (0.1)	<.0001
Median (range)	1 (0.3–1)	0.7 (0.5–1)	

Table 3Response by starting dose of 90 mg/m² vs. lower starting dose.

Response, no. (%)	Startingdose = 90 mg/m ² n = 84	Startingdose <90 mg/m ² n = 50	p-Value
OR (CR/PR/VGPR)	75 (89)	42 (88)	.78
CR	47 (56)	14 (29)	.01
VGPR	3 (4)	1 (2)	
PR	25 (30)	27 (56)	
PD/SD	9 (11)	6 (13)	
Missing	0	2	

OR: overall response; CR: complete response; VGPR: very good partial response; PR: partial response; PD: progressive disease; SD: stable disease.

Table 4

Univariable and multivariable logistic regression models for complete response.

Variable	Univariable models		Multivariable model ^a	
	Odds ratio ^b (95%CI)	Wald <i>p</i> -value	Odds ratio (95%CI)	Wald <i>p</i> -value
Starting dose at 90 mg/m ² vs. <90 mg/m ²	3.09 (1.45–6.58)	0.004	1.84 (0.75–4.50)	0.18
Age (10 year increase)	0.73 (0.54–0.98)	0.04	–	–
Male vs. female	0.46 (0.23–0.93)	0.03	0.28 (0.12–0.66)	0.004
Mantle cell lymphoma vs. non-MCL	1.02 (0.45–2.32)	0.95	–	–
ECOG PS (1 unit increase)	0.49 (0.29–0.84)	0.01	0.44 (0.24–0.82)	0.01
Stage III/IV vs. I/II	0.10 (0.01–0.80)	0.03	–	–
GFR (5 unit decrease)	0.69 (0.53–0.89)	0.005	0.70 (0.53–0.94)	0.02
Number of prior chemotherapy (1 unit increase)	0.76 (0.61–0.94)	0.01	–	–
Baseline neutropenia vs. none	0.13 (0.02–1.08)	0.06	–	–
Baseline thrombocytopenia vs. none	0.35 (0.16–0.76)	0.008	–	–

ECOG PS: Eastern Cooperative Oncology Group performance status; GFR: glomerular filtration rate.

^aOnly starting dose and other covariates with *p* < .05 using forward selection were presented in the final multivariable model.^bFor the first category of binary variables and higher values of continuous variables, an odds ratio of >1 corresponds to a higher odds of achieving CR and an odds ratio of <1 corresponds to a lower odds of achieving CR.

Table 5

Univariable and multivariable proportional hazards models for progression-free survival.

Variable	Univariable model		Multivariable model ^a	
	Hazard ratio ^b (95%CI)	Wald <i>p</i> -value	Hazard ratio (95%CI)	Wald <i>p</i> -value
Starting dose at 90 mg/m ² vs. <90 mg/m ²	0.64 (0.38–1.06)	.08	1.72 (0.93–3.20)	.09
Age (10 year increase)	1.76 (1.36–2.27)	<.0001	1.77 (1.27–2.47)	.0008
Male vs. female	1.72 (1.01–2.92)	.05	–	–
Mantel cell lymphoma vs. non-MCL	4.09 (2.41–6.92)	<.0001	3.55 (2.00–6.27)	<.0001
ECOG PS 2/3 vs. 0/1	3.22 (1.61–6.46)	.001	3.69 (1.75–7.75)	.0006
Stage III/IV vs. I/II	3.35 (0.81–13.80)	.09	–	–
GFR (5 unit decrease)	1.16 (1.03–1.31)	.02	–	–
Number of prior chemotherapy (1 unit increase)	1.10 (0.97–1.25)	.16	1.18 (1.01–1.37)	.03
Baseline neutropenia vs. none	0.93 (0.33–2.56)	.88	–	–
Baseline thrombocytopenia vs. none	1.46 (0.87–2.46)	.15	–	–

^aOnly starting dose and other covariates with $p < .05$ using forward selection were presented in the final multivariable model.

^bFor the first category of binary variables and higher values of continuous variables, a hazard ratio of >1 corresponds to a higher risk of progression or death and a hazard ratio of <1 corresponds to a lower risk of progression or death.

Table 6

Univariable and multivariable proportional hazards models for overall survival.

Variable	Univariable model		Multivariable model ^a	
	Hazard ratio ^b (95%CI)	Wald <i>p</i> -value	Hazard ratio (95%CI)	Wald <i>p</i> -value
Starting dose at 90 mg/m ² vs. <90 mg/m ²	0.59 (0.30–1.15)	.12	1.13 (0.55–2.35)	.74
Age (10 year increase)	1.53 (1.11–2.13)	.01	–	–
Male vs. female	2.33 (1.09–4.97)	.03	–	–
Mantel cell lymphoma vs. non-MCL	4.85 (2.46–9.57)	<.0001	5.60 (2.64–11.90)	<.0001
ECOG PS 2/3 vs. 0/1	6.41 (2.87–14.32)	<.0001	9.40 (3.80–23.24)	<.0001
Stage III/IV vs. I/II	3.35 (0.46–24.57)	.23	–	–
GFR (5 unit decrease)	1.22 (1.05–1.41)	.01	–	–
Number of prior chemotherapy (1 unit increase)	1.21 (1.03–1.42)	.02	–	–
Baseline neutropenia vs. none	1.99 (0.70–5.67)	.20	–	–
Baseline thrombocytopenia vs. none	2.49 (1.28–4.85)	.007	–	–

MCL: mantle cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; Chemo: lines of chemotherapeutic treatments; GFR: glomerular filtration rate.

^a Only starting dose and other covariates with $p < .05$ using forward selection were presented in the final multivariable model.

^b For the first category of binary variables and higher values of continuous variables, a hazard ratio of >1 corresponds to a higher risk of death and a hazard ratio of <1 corresponds to a lower risk of death.