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Gender specific aspects in patients with mantle cell lymphoma undergoing rituximab-based therapy – what role does gender play?

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Abstract

Background: Limited data exist on gender specific aspects in different hematologic entities including non-Hodgkin lymphomas and mucosa associated lymphoid tissue (MALT) lymphoma. The objective of this analysis was to investigate gender specific aspects in patients with mantle cell lymphoma (MCL) given therapy with Rituximab (R) plus chemotherapy in view of the suggestion of gender-differences in other lymphoma types.

Methods: In this retrospective single center evaluation, we have investigated gender specific aspects in 55 patients (female: n=11; male: n=44) with MCL, who received R - chemotherapy. Data collected from clinical records included age, sex, stage of disease, MIPI, induction therapy, autologous and allogeneic stem cell transplantation and laboratory abnormalities, respectively.

Results: Histological subtypes (common type: 91% versus 89%), ECOG performance status (0-1: 91% versus 82%), and stage III and IV disease (91% versus 93%) were equally distributed between both groups. Autologous and allogeneic stem cell transplantation showed a predominance in male patients (10 versus 0 and 4 versus 0 patients, respectively), but were most likely due to the male preponderance in the cohort. Overall survival (OS) was longer for male patients when compared to female patients (94.9 versus 40.3 months) following R-chemo, which was statistically significant (p=0.04).

Conclusion: In our cohort, gender suggested a statistically significant difference in terms of OS (p=0.04) following R-chemotherapy. All other parameters, like the three MIPI scores and stage of disease were equal between female and male gender.

Introduction

Mantle cell lymphoma (MCL) is an aggressive subtype of B-cell non-Hodgkin`s lymphoma (NHL) which accounts for approximately 6% of all NHLs [1]. Approximately 5% of patients suffer from blastic variant MCL, which is more aggressive when compared to common type MCL [2]. The most common chromosomal translocation is the t(11;14)(q13;q32), resulting in an overexpression of cyclin D1 [3]. Most patients are found to have advanced stage disease (stage III and IV) at time of diagnosis [4].

The MCL international prognostic index (MIPI) is a risk score, classifying patients in three different risk groups, i.e. low-, intermediate- and high risk group. Parameters included in the MIPI are patient age, performance status, serum lactate dehydrogenase and leukocyte count with or without Ki-67 proliferation index (MIPIc) [5].

The median overall survival with conventional chemotherapy is poor with approximately 3 years. The anti-CD20 antibody rituximab in combination with conventional chemotherapy increases the response rates, but did not increase overall survival [6].

Novel agents have been established in patients with MCL in recent years. The proteasome inhibitor bortezomib, as monotherapy as well as in different combinations [7,8], the imunomodulatory drugs (IMiDs) including lenalidomide and thalidomide [9-11] as well as bendamustine [12] or the mTOR inhibitor temsirolimus showed response rates between 31% and 81.3% [13,14].

Another therapeutic option for patients with MCL is autologous as well as allogeneic hematopoietic stem cell transplantation (HSCT). High dose chemotherapy followed by autologous HSCT in the front line setting showed promising results in young patients with MCL [15]. Allogeneic HSCT resulted in overall survival (OS) rates between 37 and 71% [16,17].

Gender specific aspects have been described in different solid tumors including bladder cancer [18] and lung cancer [19]. In hematologic malignancies, gender aspects have been described in mucosa associated lymphoid tissue (MALT) lymphomas [20] and in non-Hodgkin lymphomas in a more general way [21].

Recently, differences in terms of efficacy of R + chemotherapy between male and female patients have been suggested [22,23], which has been hypothesized to be due to different pharmacokinetics, but no such analyses have been performed for patients with MCL. In patients with follicular lymphomas (FL) female patients had a better OS when

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compared to male gender (100% versus 80% at 36 months; p=0.058), which was not significant. [22]. In the meta-analysis of Yildirim et al. male gender was associated with poor prognosis in patients with diffuse large B-cell lymphomas, who received R containing regimens [23]. In view of this, we have performed a retrospective single center study in 55 consecutive patients treated at the Medical University of Vienna.

Patients and Methods

All patients who were seen and treated with R plus chemotherapy during their course of disease at the Medical University of Vienna, Department of Oncology between July 1996 and December 2017 entered this retrospective analysis. This analysis had been approved by the local ethics board. Patients were required to have histologically confirmed MCL according to the recent WHO classification as assessed by the reference pathology of the Medical University of Vienna. Extracted data were basic characteristics, i.e. gender, performance status, mantle cell lymphoma international prognostic index (MIPI) [5], age at diagnosis stage of disease and type as well as response to first line therapy. Furthermore, dose intensity of first line treatment, autologous as well as allogeneic stem cell transplantation (SCT) and overall survival (OS) were assessed. Overall survival was calculated from time of initiation of first line treatment, i.e. R plus chemo, until death from any cause or last follow-up. OS at the time of this analysis was documented.

All patients at our department are followed on a regular basis according to a standardized protocol, resulting in the potential to provide a consistent follow-up with good adherence.

Statistical analysis

For patient data, statistical analysis was performed using a SPSS 23 software package. Continuous variables were shown using descriptive statistics. Categorical variables were summarized using percentages and counts.

For survival analysis, including OS, the Kaplan-Meier method was used. The survival curves were tested by a log-rank test. The data for patients who were alive were censored at the time of last confirmed contact. All comparisons were two-tailed and p values less than 0.05 were considered statistically significant.

Results

Patients

Fifty five patients entered this retrospective analysis. Eleven patients (20%) were female, whereas 44 patients (80%) were of male gender. Median age in the female group was 74 years (range:65-83) and 68 years (range: 44-86) in the male group. The most common subtype in both groups was the common type with 91% and 89%, respectively. Eastern Cooperative Oncology Group (ECOG) performance status (0-1) was comparable in both groups at 91% versus 82%. The majority of patients in both groups had stage III and IV disease at initial diagnosis (91% versus 93%, respectively). Intermediate and high MIPI score were most common in both groups and equally distributed at 36% versus 39% and 55% versus 40%. Laboratory abnormalities were also comparable in both groups, e.g. elevated beta-2-mikrogobulin 64% versus 58%. Baseline characteristics are outlined in Table 1.

Therapy

The most commonly used first line therapy in the female group was R-Benda (46%) and in the male group R-CHOP (52%). Dose intensity, i.e. number of cycles administered to schedule was not different, and response to first line therapy was equal in both groups (e.g. CR: 55% versus 61%). Autologous as well as allogeneic SCT was only used in male patients (10 and 4 patients, respectively). At the time of analysis, 5 female patients and 20 male patients are still alive (45% versus 46%). Detailed therapy data are outlined in table 2.

Survival

Survival data are outlined in Table 3. At the time of analysis, a statistically significance could be observed in terms of OS (p=0.04). Interestingly, MIPI low, intermediate and high risk performance status did not show statistically significance between female and male gender (p=0.128 versus p=0.129 versus p=0.125). Stage III and IV disease were equal in female and male gender in terms of OS (p=0.146) (Figure 1).

Table 1. Baseline Characteristics

Characteristic		
- Number of patients	55	
- Age (median/range)	74 (65-83)	68 (44-86)
Sex		
- Male	44 (80)	
- Female	11 (20)	
Histo	**female**	**male**
- common type	10 (91)	39 (89)
- blastic	1 (9)	5 (11)
ECOG		
0 - 1	10 (91)	36 (82)
≥ 2	1 (9)	8 (18)
Stage:		
III + IV	10 (91)	41 (93)
MIPI		
- low risk	1 (9)	9 (21)
- intermediate risk	4 (36)	17 (39)
- high risk	6 (55)	18 (40)
Laboratory abnormalities		
- LDH elevated	5 (46)	18 (40)
- Beta 2 mikroglobulin >3mg/l	7 (64)	25 (58)
- Ki67 >30%	3 (27)	17 (39)

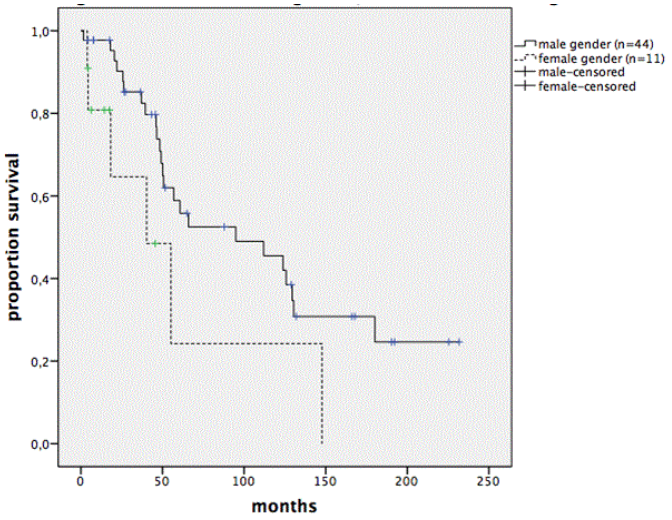

Figure 1. Overall survival gender, female versus male gender

Table 2. Prior Therapies

	Female	Male
First line therapy		
- R-CHOP	3 (27)	23 (52)
- R-Benda	5 (46)	17 (38)
- VR-CAP	2 (18)	2 (5)
- other	1 (9)	2 (5)
Response to first line therapy		
- CR	6 (55)	27 (61)
- PR	4 (36)	12 (27)
- SD	0	2 (7)
- PD	1 (9)	0
- n.a.	0	2 (5)
Second line therapy		
- BORID	2 (18)	12 (28)
- other	1 (9)	16 (36)
- no therapy	8 (73)	16 (36)
Auto KMT		
- yes	0	10 (23)
- no	11 (100)	34 (77)
Allo KMT		
- yes	0	4 (9)
- no	11 (100)	40 (91)
Status		
- alive	5 (45)	20 (46)
- dead	6 (55)	24 (54)

Table 3. Overall Survival

	Overall survival	p value
Sex		
- female	40.3 (5.9-74.6 95%CI)	0.04
- male	94.9 (17.3-172.5 95%CI)	
MIPI low risk		
- female	4.4 (95%CI n.r.)	0.128
- male	180.1 (95%CI n.r.)	
MIPI intermediate risk		
- female	147.7 (95%CI n.r.)	0.129
- male	94.9 (46.7-143.1 95%CI)	
MIPI high risk		
- female	40.3 (4.2-76.4 95%CI)	0.125
- male	48.4 (41.2-55.5 95%CI)	
Stage III + IV		
- female	55.2 (20.3-90.0 95%CI)	0.146
- male	94.9 (20.3-169.5 95%CI)	

Discussion

In this retrospective analysis, we have evaluated the role of gender on various parameters in patients with MCL who received first line therapy with R plus chemotherapy. MCL shows a male gender predominance with 70% and this is in line with our retrospective analysis (80%). In summary, we could show that histological subtype (e.g. common type: 91% versus 89%), ECOG PS 0-1 (91% versus 82%), and stage III and IV of the disease (91% versus 93%) were equally distributed between female and male patients. Furthermore, according to the MIPI, the three risk groups were comparable between female and male patients (9% versus 21%, 36% versus 39% and 55% versus 40%, respectively). Autologous and allogeneic SCT was only performed in male gender, but the numbers are too low to draw general conclusions. With the caveats of a small retraospective analysis, our data suggested that sex did significantly affect OS (p=0.04), while there was no difference in dose density of both R and chemo between genders.

Only limited data exist in terms of gender-specific features in patients with hematologic malignancies. Rituximab based chemotherapy is the standard of care in patients with MCL [6]. While non-Hodgkin lymphomas are more often diagnosed in male patients, marginal zone lymphomas and follicular lymphomas are more freqeuntly seen in female patients [21].

In a meta-analysis including 5635 patients with DLBCL treated with R containing regimens, male gender was associated with poorer prognosis when compared to female gender in terms of OS (hazard ratio (HR)=1.115;95%CI: 1.037-1.286; p<0.009) [23].

An additional study from Italy showed similar results in patients with DLBCL treated with R containing regimens as initial therapy. In this study, male gender also was a negative independent prognostic marker in multivarite analysis (p<0.001). Based on these results, the authors suggested higher doses of R in male patients. [24]

Pfreundschuh et al investigated optimal dosing of R in patients with DLBCL. In this study female patients had a better outcome than male patients, and it was reasoned that the slower R clearance in females (p=0.005) and hence higher serum levels and longer exposure times of R might explain these findings. [25]

Also in patients with follicular lymphomas (FL), higher R serum concentrations were associated with female sex (p=0.04) [22].

Another study with rituximab plus bendamustin versus bendamustin alone has also partly investigated the role of gender in various non- Hodgkin lymphomas. In this study, gender did not play a statistically signficant role in terms of survival [12].

As opposed to this, activity of IMiDs could be partly gender related according to data on lenalidomide as single agent in relapsed/refractory MCL patients. In this study, female patients appeared to be more sensitive to lenalidomide than males in terms of response (p=0.02) [10].

In an observational study conducted by the Nordic Lymphoma group analysing data from all patients with MCL treated in Denmark and Norway between 2000 and 2011, male gender was associated with impaired OS in multivariate analysis (p=0.002). Though the median age of female patients was siginifcantly higher and the rate of ASCT thus lower than in the male cohort, male patients fared worse, also in terms of respone to rituximab-based regimens which might again suggest the potential influence of gender on the pharmacokinetics of rituximab [26]. Older age as well as lower rtaes of ASCT in female patients are in line with our study. Surprisingly, in our cohort, male gender was associated with longer OS compared to female gender, when rituximab was part of therapy (94.9 versus 40.3 months;p=0.04).

In younger patients with diffuse large B-cell lymphomas (DLBCL), male gender was again associated with worse outcome in a Swedish population-based study [27], while in another study female patients had a survival advantage also in elderly patients [28].

A SEER database analysis of 5367 patients diagnosed with MCL in the US between 1992 and 2007 was conducted to investigate prognostic factors in this disease. Patients were divided in three groups according to date of diagnosis (1992-1999 versus 2000-2003 versus 2004-2007).

Conclusions

In conclusion, gender showed a statistically significant difference between females and males with respect to OS (p=0.04). All other parameters (MIPI low, intermediate and high risk) as well as stage

III and IV disease were equal in female and male gender (p=0.128, p=0.2129, p=0.125 and p=0.146, respectively).

Compliance with ethical standards

Conflict of interest

Author Lamm declares, that he has no potential conflict of interest. Author Kiesewetter declares, that she has no potential conflict of interest. Author Bauer declares, that he has no potential conflict of interest. Author Jeryczynski declares, that he has no potential conflict of interest. Author Raderer declares, that he has no potential conflict of interest.

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Ethical approval

All procedures performed in studies involving human participants were on accordance with the ethical standards of the institutional and/or national researche committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical apporval

This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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