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A registry-based analysis of survival outcomes in mast cell leukemia

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ABSTRACT

Introduction: Mast cell leukemia (MCL) is rare and carries a poor prognosis. No standard-of-care has been established. No USA registry-based analyses have examined clinical correlates of overall survival (OS) in MCL patients, thus we aimed to do this using the Surveillance, Epidemiology, and End Results (SEER) database, and the National Cancer Database (NCDB).

Materials/methods: We included 25 patients from SEER, and 50 patients from NCDB diagnosed with MCL through 2015. Kaplan-Meier and multivariable regression analyses were used to assess the impact of clinical characteristics on OS in each dataset, and on a pooled cohort of both datasets.

Results: Median age at diagnosis for the pooled cohort was 63 years, and median OS was 9.4 months. The proportion of patients surviving 12, 36, and 60 months was 42.9%, 23.2%, and 16.6%, respectively. Males (n = 44, 58.7%) outnumbered females (n = 31, 41.3%). Caucasians formed a majority (n = 66, 88%). With Cox regression accounting for database of origin, age at and year of diagnosis, sex, race, sequence number, and receipt of chemotherapy, no variable was significantly associated with OS. However, in the same analysis, when stratified by sex, receipt of chemotherapy was associated with improved OS in males (HR = 0.41, 95% CI 0.14-0.89, $p < 0.03$), and poorer OS in females (HR = 3.64, 95% CI 1.07–12.44, p = 0.04).

Conclusions: Our study reaffirms that MCL carries a poor prognosis. Chemotherapy may improve survival in subsets of patients, though generalizability is limited by biases inherent in registry-based datasets. Due to poor outcomes for MCL patients, more study is needed to determine optimal care.

1. Introduction

Mast cell leukemia (MCL) is a rare myeloid malignancy that exists on the severe end of the spectrum of systemic mastocytosis (SM) accounting for < 1% of all SM in the USA [1]. It is a disease characterized by leukemic or aleukemic spread of mast cells, and can involve not only the bone marrow, but visceral organs as well [23]. Diagnosis is based on World Health Organization (WHO) criteria updated in 2016 [2]. The primary diagnostic hallmark of MCL is 20% or greater mast cells present on bone marrow biopsy [2]. In addition, a distinction of chronic versus acute MCL has been incorporated in the WHO diagnostic criteria [23]. MCL was first described as early as 1906 [4]. MCL can occur *de novo*, or secondarily in a background of SM [5–7]. Prior retrospective studies have reported that MCL carries a grave prognosis [5–7]. MCL is noted to relapse frequently after therapy [5–7]. Standard-of-care therapy for MCL has not been firmly established as no prospective studies of therapy for MCL have been completed. To date, no USA registry-based studies of MCL outcomes have been conducted. Thus it was our aim to assess the demographic and clinical correlates of overall survival (OS) in MCL using data from the Surveillance, Epidemiology, and End Results (SEER) database, and the National Cancer Database (NCDB).

2. Methods/materials

From the SEER 18 registries we included 25 patients diagnosed with MCL between 1988 and 2015. From the NCDB we included 50 patients with MCL diagnosed between 2004 and 2015. Cases were defined by International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) histology code 9742/3 “Mast cell leukemia” [8]. On review of the raw data we identified 4 cases in the SEER dataset which had significant overlap in demographic and survival information between corresponding cases in NCDB. Given the rarity of MCL, these likely represented patients registered in both databases. To prevent the inclusion of duplicated patients we removed the 4 cases from our final SEER cohort and retained the corresponding NCDB cases as these included more information. Removing these 4 patients from the SEER cohort did not significantly alter the OS or MCL-specific survival outcomes we report. All of the included patients had complete survival information. Data from each database were analyzed individually, and as a pooled

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Table 1
Patient and treatment characteristics by cohort.

Variable	NCDB + SEER		NCDB		SEER	
	n	%	n	%	n	%
Total	75	100.0	50	100.0	25	100.0
Database						
SEER	25	33.3	–	–	–	–
NCDB	50	66.7	–	–	–	–
Age						
0-19	3	4.0	3	6.0	0	0.0
20-29	7	9.3	3	6.0	4	16.0
30-39	6	8.0	4	8.0	2	8.0
40-49	6	8.0	4	8.0	2	8.0
50-59	8	10.7	7	14.0	1	4.0
60-69	19	25.3	11	22.0	8	32.0
70-79	18	24.0	12	24.0	6	24.0
≥80	8	10.7	6	12.0	2	8.0
p value¶	–		0.86			
Median age (years)	63		62		63	
Minimum age (years)	13		13		23	
Maximum age (years)	88		88		88	
Sex						
Male	44	58.7	30	60.0	14	56.0
Female	31	41.3	20	40.0	11	44.0
p value£	–		0.74			
Race						
White	66	88.0	45	90.0	21	84.0
Black	5	6.7	2	4.0	3	12.0
Other^	4	5.3	3	6.0	1	4.0
p value£	–		0.41			
Year of diagnosis	1988-2015		2004-2015		1988-2015	
MCL sequence						
De novo	53	70.7	34	68.0	20	80.0
Secondary	22	29.3	16	32.0	5	20.0
p value£	–		0.47			
Chemotherapy						
No	34	45.3	21	42.0	13	52.0
Yes	41	54.7	29	58.0	12	48.0
p value£	–		0.41			
Radiation						
No	–	–	48	96.0	25	100.0
Yes	–	–	2	4.0	0	0.0
p value£	–		0.31			
Hormone therapy						
No	–	–	46	92.0	–	–
Yes	–	–	4	8.0	–	–
Immunotherapy						
No	–	–	47	94.0	–	–
Yes	–	–	3	6.0	–	–
Transplant						
No	–	–	47	94.0	–	–
Yes, autologous	–	–	1	2.0	–	–
Yes, allogeneic	–	–	1	2.0	–	–
Yes, unknown type	–	–	1	2.0	–	–
Other therapy						
No	–	–	45	90.0	–	–
Yes	–	–	5	10.0	–	–
Palliative therapy						
No	–	–	45	90.0	–	–
Yes	–	–	5	10.0	–	–
Charlson-Deyo comorbidity score						
0	–	–	37	74.0	–	–
1	–	–	11	22.0	–	–
2	–	–	2	4.0	–	–
Treatment facility type						
Community cancer program	–	–	2	4.0	–	–
Comprehensive community cancer program	–	–	12	24.0	–	–
Academic/research program	–	–	21	42.0	–	–
Integrated network cancer program	–	–	5	10.0	–	–
Unknown	–	–	10	20.0	–	–

Legend. ^Includes Asian, Native American, Alaska Native/Pacific Islander. ¶p value from two sample *t*-test with age as a continuous variable. £p value from chi-square test.

cohort retaining variables that are shared between SEER and NCDB. Categorical variables were summarized as counts and percentages and were compared with chi-square tests. Continuous variables were compared between cohorts with t-tests. Kaplan-Meier curves and log-rank tests were used to assess OS differences between groups. Univariable and multivariable Cox proportional hazards models were utilized to assess the effects of clinical and demographic characteristics on OS. Proportional hazards assumptions for the Cox regression model were tested and met as per the Schoenfeld residual method [9]. All statistical analyses were conducted using STATA 14 software [10]. All p values were two-sided with a 0.05 threshold for significance. Propensity score matching, which has been used extensively in NCDB analyses to minimize confounders which influence treatment selection, was not practical to employ in this analysis, given the small number of patients included.

3. Results

3.1. Patient characteristics

Table 1 summarizes patient characteristics at the time of MCL diagnosis. Age distributions were similar between the NCDB and SEER cohorts (*t*-test p = 0.86). Patient sex and race counts were also similar between the NCDB and SEER cohorts (chi-square test p = 0.41 and p = 0.74, respectively). Median age for the pooled cohort was 63 years (range 13–88 years). Males outnumbered females (n = 44, 58.7%, and n = 31, 41.3%, respectively). Caucasian patients formed a majority of the cases (n = 66, 88%). *De novo* MCL, as determined by the "Sequence number" field in the NCDB, or "First malignant primary indicator" field in SEER, accounted for 70.7% of MLC cases (n = 53), with secondary (or higher order) MCL accounting for 29.3% (n = 22). The distribution of *de novo* versus secondary cases of MCL did not differ significantly between the SEER and NCDB cohorts (chi-square test p = 0.47).

Additional demographic characteristics coded only in the NCDB database are also summarized in Table 1. Most patients in the NCDB cohort had a Charlson-Deyo comorbidity score of 0 (n = 37, 74% of NCDB total). A plurality of patients were treated at an academic cancer center (including National Cancer Institute designated comprehensive cancer centers) or a comprehensive community cancer center (n = 21, 42%, and n = 12, 24%, of NCDB total, respectively).

3.2. Treatment characteristics

Treatment information is summarized in Table 1. The information coded on treatment encompasses more modalities and is more granular in NCDB than in SEER. The coding of specific treatments received is explained in detail in the NCDB data dictionary (http://ncdbpuf.facs.org/node/259?q) and the SEER coding manual (https://seer.cancer.gov/manuals/2018/SPCSM_2018_maindoc.pdf). For the combined cohort we were able to determine receipt of chemotherapy for MCL, or not, for all patients, with the caveat that SEER uses the description of no or unknown chemotherapy administration due to under-reporting of chemotherapy use. In total chemotherapy was given to 41 patients (54%). No patients in either database were coded as having received a cancer-directed surgical procedure in the management of MCL. Few patients in the NCDB cohort (n = 2, 4% of NCDB total) and no patients

Table 2
Survival analysis: Comparison of OS probabilities and Cox regression analyses in the pooled SEER and NCDB cohort and MCL-specific survival in the SEER cohort.

Variable	n	%	Median OS (months)	12 month OS (%)	36 month OS (%)	60 month OS (%)	Univariable analysis*			Multivariable analysis*		
							HR	95% CI	p value	HR	95% CI	p value
Total	75	100.0	9.4	42.9	23.2	16.6	–	–	–	–	–	–
Database												
SEER	25	33.3	14	48.0	21.1	15.8	0.78	0.43-1.40	0.41	0.65	0.29-1.46	0.30
NCDB	50	66.7	8.2	40.0	24.0	20.6	–	–	–	–	–	–
p value†	p = 0.40											
Sex												
Male	44	58.7	10.9	47.6	23.2	–	–	–	–	–	–	–
Female	31	41.3	6.9	39.3	23.2	5.8	1.21	0.70-2.12	0.48	1.22	0.69-2.17	0.48
p value†	p = 0.48											
Race												
White	66	88.0	10.9	46.8	23.1	15.9	–	–	–	–	–	–
Black	5	6.7	1.5	20.0	–	–	1.59	0.57-4.46	0.37	1.95	0.61-6.31	0.26
Other^	4	5.3	0.8	25.0	–	–	1.56	0.38-6.47	0.54	1.87	0.35-10.12	0.47
p value†	p=0.56						1.01	0.97-1.06	0.44	1.00	0.94-1.06	0.93
Chemotherapy												
No	34	45.3	8.2	40.6	27.1	22.6	–	–	–	–	–	–
Yes	41	54.7	10.9	47.4	20.1	16.1	1.06	0.61-1.85	0.83	1.01	0.55-1.87	0.97
p value†	p = 0.83											
MCL sequence												
De novo	53	70.7	8.0	42.0	27.2	20.7	–	–	–	–	–	–
Secondary	22	29.3	10.9	50.0	13.3	6.7	1.31	0.74-2.34	0.35	1.23	0.66-2.30	0.51
p value†	p = 0.35											
Died from MCL‡												
No	12	48.0	21.0	71.4	29.6	–	–	–	–	–	–	–
Yes	13	52.0	6.0	18.8	9.1	–	–	–	–	–	–	–
p value†	< 0.01											

Legend. †p values from two-tailed log-rank test. ^Includes Asian, Native American, Alaska Native/Pacific Islander. ‡ Includes patients from the SEER cohort only as cause of death information is not available in NCDB. *Hazard ratio (HR), 95% confidence interval (95% CI), and p value from univariable Cox proportional hazards model or multivariable Cox proportional hazards model accounting for database of origin, age at and year of diagnosis, sex, race, and sequence of MCL.

in the SEER cohort received MCL-directed radiation therapy. Hormonal therapy (i.e., corticosteroid) was administered to 4 patients in NCDB as part of their chemotherapy regimen. Few patients received immunotherapy (n = 3, 6% of NCDB total) or underwent stem cell transplant (n = 3; 1 allogeneic; 1 autologous; 1 unknown type, 6% of NCDB total). The "Other treatment" field in NCDB includes treatments which do not fall within the definitions of surgery, radiation, or systemic therapy; in the NCDB cohort 1 patient (2%) received "other-experimental" treatment, which is not defined further, and 4 (8%) received supportive care treatments "unique to hematopoietic diseases", which are not defined further. Palliative treatments are also included in the NCDB; 1 patient (2%) received palliative radiation therapy, 3 patients (6%) received palliative systemic therapy, 1 patient (2%) received palliative treatment not defined further.

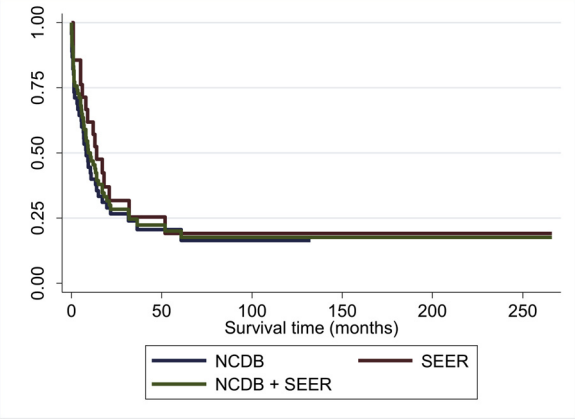

Fig. 1. Kaplan-Meier OS estimates for MCL patients by database.

3.3. Survival analysis

Table 2 depicts summarized survival data and Cox proportional hazards regression analyses for the pooled cohort and Fig. 1 depicts the Kaplan-Meier OS curves for the SEER, NCDB, and pooled cohorts. Median OS for the pooled cohort was 9.4 months (95% CI 6.7–14.9 months). The proportion of patients surviving 12, 36, and 60 months was 42.9%, 23.2%, and 16.6%, respectively. Median OS was not significantly different between the SEER and NCDB cohorts (log-rank test p = 0.40). With Cox regression accounting for database of origin, age at and year of diagnosis, sex, race, sequence number, and receipt of chemotherapy for MCL, no single variable was significantly associated with OS. However, in the same analysis, when stratified by patient sex, receipt of chemotherapy was associated with improved OS in males (HR = 0.41, 95% CI 0.14-0.89, p < 0.03), and an OS decrement in females (HR = 3.64, 95% CI 1.07–12.44, p = 0.04), this is shown in Table 3. MCL specific survival was computed with the SEER cohort alone, as this database includes cause of death information. The majority of patients in the SEER cohort died from MCL (n = 13, 52% of SEER total), median survival for those who died from MCL was 6.0 months compared to 21.0 months for those who died from other causes, this was a significant difference (log-rank test p < 0.01).

4. Discussion

4.1. Patient characteristics

This study represents the first USA registry-based analysis of outcomes in MCL. It is also the single largest cohort of MCL cases analyzed to date. Several findings in our study depart from those of prior studies. The largest published series to date prior to the current study included 51 MCL cases pooled from across multiple published case reports and case series and reported a female predominance (Female to male = 1.5 to 1) and a median age at diagnosis of 51 years [6]. In the present study there was a male to female predominance of roughly 1.5–1, and an

Table 3
Cox proportional hazards regression analysis: OS survival impact of receipt of chemotherapy by patient sex in the pooled SEER and NCDB cohort.

	Chemotherapy	n	Median OS (months)	HR	Univariable analysis*			Multivariable analysis*	
					95% CI	p value	HR	95% CI	p value
Male									
	No	23	5.0	–	–	–	–	–	–
	Yes	21	14.9	0.52	0.25-1.07	0.08	0.41	0.19-0.89	0.024
Female									
	No	11	32.0	–	–	–	–	–	–
	Yes	20	5.0	2.91	1.13-7.51	0.03	3.64	1.07-12.44	0.04

Legend. *Hazard ratio (HR), 95% confidence interval (95% CI), and p value from univariable Cox proportional hazards model or multivariable Cox proportional hazards model accounting for database of origin, age at and year of diagnosis, race, and sequence of MCL.

older median age at diagnosis by over a decade (63 years). These differences may reflect biases in what types of patients are presented for case reports or series.

The distribution of *de novo* versus secondary MCL cases in the current study (70.7% *de novo*, 39.3% secondary) matches that reported in the aforementioned series of 51 cases (70% *de novo*) [6]. Also mirrored in the present study is the predominance of MCL cases in Caucasians (88% in the present study versus 85% in the previously reported series). For the 50 patients included in the present study from the NCDB, a Charlson-Deyo comorbidity score was available, and the majority of these patients (n = 37, 74% of NCDB total) had a score of 0, which implies that they had no significant medical comorbidities present at the time of MCL diagnosis [11]. These data speak indirectly to the performance status (PS) of patients with MCL, though more accepted oncology-specific measures of PS such as Eastern Cooperative Oncology Group (ECOG) PS, and Karnofsky PS (KPS) are not available in SEER or NCDB.

4.2. Survival

The OS outcomes we report are poor, with a median OS of 9.4 months. This is higher than those reported in the next largest series to date (6 month median OS), however that study included cases dating back to 1950 [6], whereas ours dates back to 1988, with the majority of cases diagnosed after 2000 (Table 1), and thus the improved median OS seen here may be an effect of improvements in treatment and supportive care for MCL patients. Patients in other small to moderate sized modern series experienced improved median OS relative those in our study; 17 months in single institution series from Germany [5] and 31 months in a US series [7]. These OS differences across series may correlate with a higher prevalence of more aggressive MCL (based on severity of underlying SM, or cytogenetic markers) as suggested by the authors of the MD Anderson Cancer Center experience [7]. No significant demographic correlates of OS were identified on multivariable Cox regression analysis in the present study; this may be an effect of small sample size.

4.3. Treatment

No single standard-of-care exists for MCL patients. This is a consequence of the scarcity of the disease and the absence of prospective therapeutic trials pertaining specifically to MCL. Algorithms for care have been suggested [3], although no single therapeutic agent or procedure has been reported to be curative. The role of targeted therapies based on molecular drivers of SM and MCL, such as c-KIT mutations, in particular the D816 V mutation, is an open area of investigation, with results showing promise in SM [12–15]. Midostaurin and imatinib, two targeted agents with established indications for use in SM have been used in MCL with mixed results [13–17]. Gemtuzumab ozogamicin a monoclonal antibody-drug conjugate, has shown promise in advanced SM and there is a published case report of a complete response in a patient with treatment refractory MCL [1819]. The role of hematopoietic stem cell transplant is also unclear, with only a few case reports of prolonged survival in MCL patients who undergo them [56,20–25]. Immunotherapies such as corticosteroids and interferon-alpha have established uses in the management of SM and have been used in MCL patients as well with less success [6,26–30]

Cytotoxic chemotherapy has been used with varying success to decrease mast cell burden in SM and to treat MCL [30–37]. In our study we examined the effect of cytotoxic chemotherapy on OS pooled between the NCDB and SEER cohorts. The specific number and type of agents used was not available in either database. Lacking chemotherapy specifics, we were bound to reduce the receipt-of-chemotherapy to a binary variable; yes or no/unknown. On multivariable analysis, including all patients, chemotherapy for MCL was not a significant correlate of OS (Table 1), but when stratified by sex chemotherapy was associated with significantly improved OS in men, and a significant survival decrement in women (Table 3). This finding suggests that chemotherapy may have a role in improving outcomes in subsets of MCL patients. Moreover, greater than 50% of patients in our study received chemotherapy, demonstrating that it is has been frequently used in MCL patients, though as previously mentioned, newer targeted agents for MCL are available and are included in the most contemporary treatment guidelines, and many of the patients included in our study pre-date the development of these agents [3]. Whether sex-dependent difference in survival with chemotherapy we observe reflects true biological differences in disease severity between sexes or selection biases in a small sample is speculative.

Other therapies accounted for in NCDB, such as radiation therapy, immunotherapy, and stem cell transplant, were not analyzed for impact on OS, as they were too infrequently utilized in our sample to contribute meaningfully to multivariable analysis.

4.4. Limitations

Our study is subject to the limitations inherent in all retrospective, registry-based analyses. This is compounded in our study by relatively small numbers compared to comparably executed studies of outcomes with SEER and NCDB data that include more patients, which facilitates more complex statistical analyses and more robust results [38]. The rarity of MCL is limiting. In addition, there are significant missing covariables in these databases; there is no information on the specifics of systemic therapy agents used, there is incomplete socio-economic and demographic information, and there is no integration of tumor genetic and immunologic profiling, which all may carry significant prognostic weight in MCL. This is salient information to possess as the paradigms of ‘personalized medicine’ extend into the realm of the less common malignancies.

5. Conlcusions

This hypothesis-generating study, the largest series of MCL cases

reported to date, reaffirms that MCL carries a poor prognosis. We suggest here that chemotherapy may improve survival outcomes in subsets of patients, though our analysis is limited by small sample size and significant selection biases inherent in registry-based datasets.

In light of the poor outcomes for MCL patients overall and the rarity of the disease, collaborative efforts should be undertaken to accumulate comprehensive data on MCL patient, tumor and treatment characteristics as well as survival outcomes at the national or international level. Further study of MCL patients is needed to determine optimal therapeutic regimens. Given the rare incidence of MCL, options for prospective study may be limited, though international pooled analyses may be feasible.

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Conflicts of interest

None.

CRediT authorship contribution statement

Justin Budnik: Conceptualization, Methodology, Project administration, Data curation, Formal analysis, Writing - original draft. **Michael T. Milano:** Conceptualization, Methodology, Writing - review & editing.

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