

Differential Outcomes Among Immunosuppressed Patients With Merkel Cell Carcinoma

Impact of Immunosuppression Type on Cancer-specific and Overall Survival

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Objectives: Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer with higher incidence among whites, elderly, and immunosuppressed patients. Although immunosuppressed MCC patients are at higher risk of recurrence and MCC-related death, it is unknown whether immunosuppression type is associated with differential outcomes.

Materials and Methods: We retrospectively evaluated 89 non-metastatic MCC patients with a diagnosis of chronic immunosuppression. Immunosuppression was categorized as chronic lymphocytic leukemia (31% of cohort), other hematologic malignancies (18%), solid organ transplant (21%), autoimmune disease (21%), and human immunodeficiency virus acquired deficiency syndrome (8%). Progression-free survival (PFS) and MCC-specific survival (MSS) were estimated with the cumulative incidence function. Overall survival (OS) was estimated by the Kaplan-Meier method.

Results: With a median follow-up of 52 months, 53 deaths occurred (42 from MCC, 7 unknown, and 4 non-MCC). Two-year PFS, MSS, and OS were 30%, 55%, and 52%, respectively. Human immunodeficiency virus/acquired deficiency syndrome and solid organ transplant patients were diagnosed with MCC at a younger age (median 55 and 59 y, respectively) and with more advanced stage disease compared with other immunosuppressed subgroups. PFS did not significantly differ among the 5 immunosuppression subgroups ($P=0.30$), but significant differences were observed in MSS and OS (both $P=0.01$). Controlling for potential confounders for OS, including age and stage, immunosuppression type was still significantly associated with risk of death ($P=0.01$).

Conclusions: Among immunosuppressed MCC patients, recurrent MCC is the major cause of mortality. The risk of death from MCC differs among immunosuppression types, suggesting important biological differences in host-tumor immune interactions.

Key Words: Merkel cell carcinoma, immunosuppression, HIV/AIDS, CLL, solid organ transplant, outcomes

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Merkel cell carcinoma (MCC) is a malignant neuroendocrine skin cancer with a high propensity for recurrence and metastasis. Risk factors for MCC include age above 50 years, chronic immunosuppression, and UV exposure.^{1–3} The Merkel cell polyomavirus (MCPyV) is associated with MCC in ~60% to 80% of patients,⁴ suggesting a prominent role of the immune system in this cancer. Although most individuals are exposed to MCPyV, very few develop MCC due to immune surveillance mechanisms. However, an immunosuppressed state may facilitate the various steps of MCPyV integration, mutagenesis, and carcinogenesis. The immune system also plays an important role in UV-radiation-associated MCC. In addition to inducing immune suppression through suppressor T cells, UV-radiation facilitates carcinogenesis through introduction of DNA photoproducts and mutagenesis. In an immunosuppressed host, impaired immunosurveillance may then permit tumor development and growth.⁵ Chronic immunosuppression, including use of immunosuppressive drugs, is associated with increased risk of cutaneous malignancies, including MCC.^{1,6,7} Indeed, immunosuppressed individuals are disproportionately represented among MCC patients compared with that of the immune competent population.

Rates of chronic immunosuppression among patients with MCC vary across series, but appears to be roughly 10% among single-institution cohorts.^{8–10} human immunodeficiency virus (HIV)/acquired deficiency syndrome (AIDS),¹ lymphoproliferative disorders including chronic lymphocytic leukemia (CLL),¹¹ solid organ transplantation (SOT),¹² and autoimmune diseases¹³ have all been associated with increased risk of MCC. Furthermore, it is well established that compared with immune competent patients with MCC, immunosuppressed MCC patients have significantly worse MCC-specific survival (MSS) and overall survival (OS).^{8–11,14,15}

Although outcomes among immunosuppressed patients with MCC are poor, it is unknown whether immunosuppression type affects cancer outcomes. Given that the immune system is thought to be an important mediator for MCC control, we hypothesized that type of chronic immunosuppression is differentially associated with MSS and OS.

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MATERIALS AND METHODS

Description of Cohort and Eligibility

The cohort was identified from a Seattle-based registry of patients enrolled between 2002 and 2016 with pathologically confirmed MCC. All enrolled patients provided informed consent for release of medical records and future contact. Set protocols were followed for data entry and patient updates. Patients were regularly followed at least annually by email and/or phone for changes in disease status, treatments, and survival. Information regarding immunosuppression (type, date of diagnosis, immunosuppressive drugs) was abstracted from medical records. Review of patient records was performed in accordance with the Fred Hutchinson Cancer Research Center institutional review board.

Eligible patients for this study met the following criteria: (1) MCC confirmed histologically; (2) age above 18 years; (3) no evidence of distant metastatic MCC disease at presentation (ie, stages I to III); (4) chronic immunosuppression present at the time of MCC diagnosis or diagnosed within 1 year after MCC diagnosis; and (5) initial treatment with curative intent. Curative (versus palliative) intent treatment was determined based on use of surgery and/or radiation in accordance with NCCN treatment guidelines.¹⁶

Chronic immunosuppression was categorized as CLL, other hematologic malignancy (OHM), autoimmune disease (AD), or SOT. CLL was considered a distinct immunosuppression category from OHMs based on data suggesting differences in risk and outcomes between these 2 groups.^{11,17} OHMs included non-Hodgkin's lymphomas, multiple myeloma, and mycosis fungoides. Autoimmune diseases included rheumatoid arthritis, lupus, Crohn disease, ulcerative colitis, and Lambert-Eaton Syndrome.

Treatment

Radiation treatment was routinely given to the local and/or nodal sites based on the discretion of the treating radiation oncologist. At diagnosis, patients underwent excisional biopsy. Additional surgery, which included wide-local excision or Mohs, was performed based on margin status and/or whether radiotherapy would be utilized.

Statistical Analyses

Endpoints for this study were MCC-specific progression-free survival (PFS), MSS, and OS. All endpoints for statistical analyses were calculated from the date of diagnosis (initial biopsy date). Living patients were censored from all analyses at the date of last follow-up. We evaluated for differences in PFS, MSS, and OS among the immunosuppression types. Given the high risk of death from medical comorbidities, a competing risk analysis with the cumulative incidence function was used to calculate PFS and MSS, and differences in PFS and MSS were assessed with the Gray test. MCC recurrence and death from MCC were events for PFS; MCC-specific death was an event for MSS. Non-MCC death was a competing risk. For 6 patients, cause of death was unknown; 3 of these 6 patients had MCC recurrence. All 6 patients with unknown cause of death were included as deaths from MCC given the high likelihood of death from MCC over non-MCC causes, especially in the setting of recurrent disease.¹⁸ OS was calculated using the Kaplan-Meier method, and differences between immunosuppression types were evaluated with the log-rank test.

Time to first recurrence was recorded and categorized as local (within 5 cm from primary site), in-transit, regional (draining lymph node basin), or distant (beyond draining lymph

node basin). Of note, a local recurrence in an irradiated patient could potentially reflect an in-field, marginal miss, or a complete miss as radiation-specific fields were not available for all patients for verification.

Final covariates for the multivariate Cox regression models for PFS, MSS, and OS included age, stage, immunosuppression type, and time from diagnosis to registry enrollment (ie, enrollment lag time). The latter covariate was included based on previous findings that delayed time from diagnosis to registry enrollment is associated with poor patient outcomes.¹⁰ Given very similar multivariate analysis results for MSS and OS, only results for OS are presented. Analyses were performed with SAS (version 9.4). $P < 0.05$ were considered statistically significant, and all tests were 2-sided.

RESULTS

Patient Cohort

Of 969 patients from the Seattle-based MCC data repository, 109 (11%) had a diagnosis of chronic immunosuppression. In total, 89 immunosuppressed patients had nonmetastatic disease and were eligible for our analysis. Comparison of immunosuppressed and immune competent patients is reported separately.¹⁹ The most common immunosuppression subtype was CLL (n = 28), followed by SOT (n = 19), AD (n = 19), OHM (n = 16), and HIV/AIDS (n = 7). Median duration of immunosuppression was 100 months (range, 6 to 536 mo). At diagnosis, most CLL, AD, and OHM patients presented with primary disease that did not involve regional lymph nodes (ie, stage I/II). In contrast, 100% HIV/AIDS and 58% SOT patients had stage III (regional lymph node involvement) disease at diagnosis (Table 1). Median age at diagnosis was lower for HIV/AIDS (55 y) and SOT (59 y) compared with CLL, OHM, and AD (all 71 y).

All SOT patients (100%) and most AD patients (89%) were taking at least 1 immunosuppressive medication at the time of MCC diagnosis. For SOT patients, the most common immunosuppressive medications were mycophenolic acid, sirolimus, azathioprine, prednisone, tacrolimus, and cyclosporine. The most common medications for AD patients were hydroxychloroquine, prednisone, methotrexate, azathioprine, and cyclosporine.

Treatment received was generally similar across immunosuppression subtypes. Most (86%) received conventionally fractionated radiation treatment with 97% and 70% receiving local and regional radiotherapy, respectively, to a median dose of 5025 cGy (range, 3750 to 7000 cGy). Almost all immunosuppressed MCC patients, except for MCC patients with HIV/AIDS, underwent surgery after initial biopsy (Table 1).

Outcomes

With a median follow-up of 52 months (range, 2 to 135 mo) among living patients, 53 deaths occurred: 42 from MCC, 4 non-MCC, and 7 unknown causes. Two-year PFS, MSS, and OS were 30%, 55%, and 52%, respectively. PFS, MSS, and OS estimates by immunosuppression type are summarized in Table 2. Median PFS for the entire cohort was 10 months. PFS was not significantly different ($P = 0.30$) between immunosuppression types (Fig. 1).

In contrast, MSS was significantly different between immunosuppression types (Fig. 2; $P = 0.01$). HIV/AIDS and SOT patients had worse MSS (Table 2) compared with other immunosuppression types; 6 of 7 HIV/AIDS patients died from MCC. MSS differences translated to significant differences in OS ($P = 0.01$; Fig. 3).

Given the differences in MSS and OS between immunosuppression types despite no significant differences in PFS, we

TABLE 1. Demographic, Pathologic, and Treatment Characteristics of Immunosuppressed MCC Patients by Immunosuppression Type

	HIV/AIDS (N = 7)	Chronic Lymphocytic Leukemia (N = 28)	Autoimmune Disease (N = 19)	Solid Organ Transplant (N = 19)	Other Hematologic Malignancies (N = 16)	P
Median age at diagnosis (range)	55 (45-64)	71 (53-91)	71 (37-82)	59 (40-76)	71 (54-84)	< 0.001
Sex (n [%])						
Female	1 (14)	7 (25)	7 (37)	6 (32)	4 (25)	0.82
Male	6 (86)	21 (75)	12 (63)	13 (68)	12 (75)	—
MCC stage (n [%])						
I-II (local)	0 (0)	18 (65)	13 (68)	8 (43)	13 (81)	0.002
III (nodal/regional)	7 (100)	10 (36)	6 (32)	11 (58)	3 (19)	—
Chemotherapy (n [%])						
No	5 (71)	24 (86)	12 (63)	15 (83)	16 (100)	0.05
Yes	2 (29)	4 (14)	7 (37)	3 (17)	0 (0)	—
Radiation therapy (n [%])						
No	0 (0)	5 (18)	1 (5)	3 (17)	3 (19)	0.59
Yes	7 (100)	23 (82)	18 (95)	15 (83)	13 (81)	—
Surgery (n [%])						
No	2 (33)	1 (4)	0 (0)	0 (0)	2 (13)	0.02
Yes	4 (67)	25 (96)	16 (100)	18 (100)	13 (87)	—

Bold indicates significant *P* value.

HIV/AIDS indicates human immunodeficiency virus/acquired deficiency syndrome; MCC, Merkel cell carcinoma.

hypothesized that there may be differences in patterns of first failure across the immunosuppression types and that patients with certain immunosuppression types may undergo successful salvage therapy. The most common first failure was local (2 y rates: 25%), followed by distant (21%), regional (16%), and in-transit (3%). We evaluated the patterns of first recurrence by type of chronic immunosuppression (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/AJCO/A224>). MCC patients with HIV/AIDS had a predominance of distant first recurrence, in comparison to MCC patients with CLL, SOT, or AD, of which ~50% had a local or regional first recurrence.

Salvage Therapy After Recurrence

Among those MCC patients with recurrent disease and available data (n = 61), 64% received treatment after recurrence

including surgical resection (43%; ie, beyond a biopsy), radiation (54%), chemotherapy (36%), and immunotherapy (5%). Radiotherapy data were only available among 14 of 33 irradiated patients and was heterogenous (median, 41.5 Gy; range 8 to 70 Gy). All 42 MCC patients that died had distant disease at death, although 25 of these patients (60%) initially presented with a local, in-transit, or regional first recurrence.

To evaluate whether aggressive therapy after recurrence impacts disease remission, PFS among recurrent MCC patients that did or did not receive surgery or immunotherapy were calculated. PFS rates for recurrent MCC patients treated with radiotherapy were not performed given the heterogenous radiation doses that likely reflected a mix of curative and palliative-intent treatment. Two-year PFS after relapse among those MCC patients that received salvage surgery was 12% versus 6%

TABLE 2. Kaplan-Meier and Cumulative Incidence Function Estimates for PFS, MSS, and OS by Immunosuppression Type

	HIV/ AIDS	Chronic Lymphocytic Leukemia	Solid Organ Transplant	Autoimmune Disease	Other Hematologic Malignancy
PFS					
Median (mo)	7.4	10.3	9.5	15.3	12.2
6 mo (%)	71	78	79	74	87
1 y (%)	14	45	33	53	50
2 y (%)	—	33	16	42	46
MCC-specific survival					
Median (mo)	16.4	26.6	22.1	NR*	40.0
6 mo (%)	86	100	89	100	100
1 y (%)	71	85	79	83	87
2 y (%)	0	62	45	72	60
OS					
Median (mo)	16.4	26.6	22.1	NR*	40.0
6 mo (%)	86	100	84	100	100
1 y (%)	71	85	73	83	88
2 y (%)	0	62	40	67	60

*Median value not reached.

HIV/AIDS indicates human immunodeficiency virus/acquired deficiency syndrome; MCC, Merkel cell carcinoma; NR, not reached; OS, overall survival; PFS, progression-free survival.

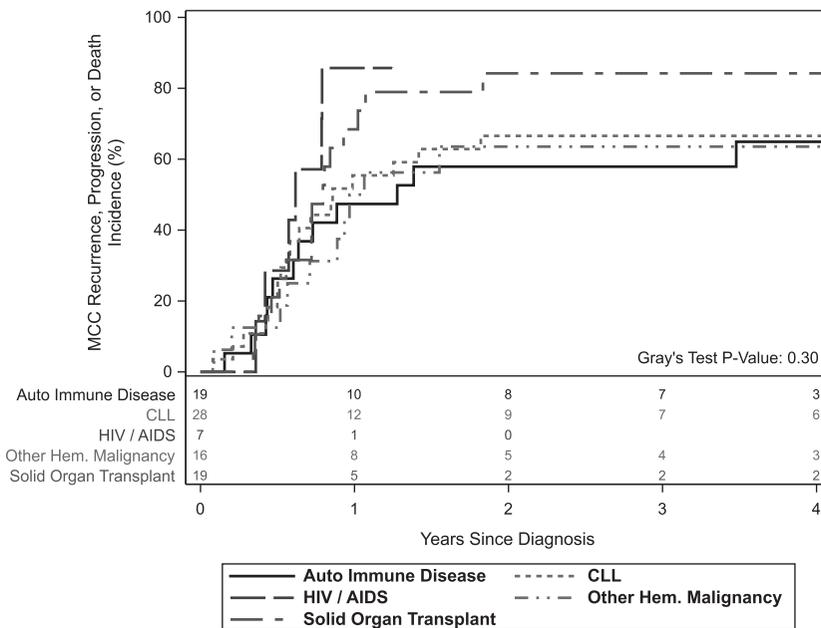


FIGURE 1. Cumulative incidence function of MCC progression-free survival among immunosuppressed patients by immunosuppression type. CLL indicates chronic lymphocytic leukemia; MCC, Merkel cell carcinoma.

among those that did not undergo surgery. Three received salvage immunotherapy with a 2-year PFS of 0%, versus 9% for those that did not receive salvage immunotherapy. Relapsed MCC patients that remain alive include those that had a first recurrence that was local (1 CLL, 2 AD, 1 SOT), regional (1 AD, 2 OHM), in-transit (1 OHM), and metastatic (1 CLL, 1 SOT, 2 OHM).

Prognostic Factors

On multivariate Cox regression analysis controlling for lag time from enrollment, stage at diagnosis, and age, immunosuppression

type remained an independent predictor for OS ($P=0.01$; Table 3). Similar results were obtained when evaluating for significant predictors of MSS on multivariate analysis (results not shown). In contrast, the only significant predictor for PFS was lag time to enrollment (Table 3), in which patients that were enrolled > 180 days from diagnosis had worse PFS (hazard ratio, 1.81; 95% confidence interval, 1.08-3.03). This is consistent with our clinical observations, in which MCC patients with relapsed/refractory disease present to our institution for a second opinion and treatment options. Immunosuppression type was not significantly associated with PFS.

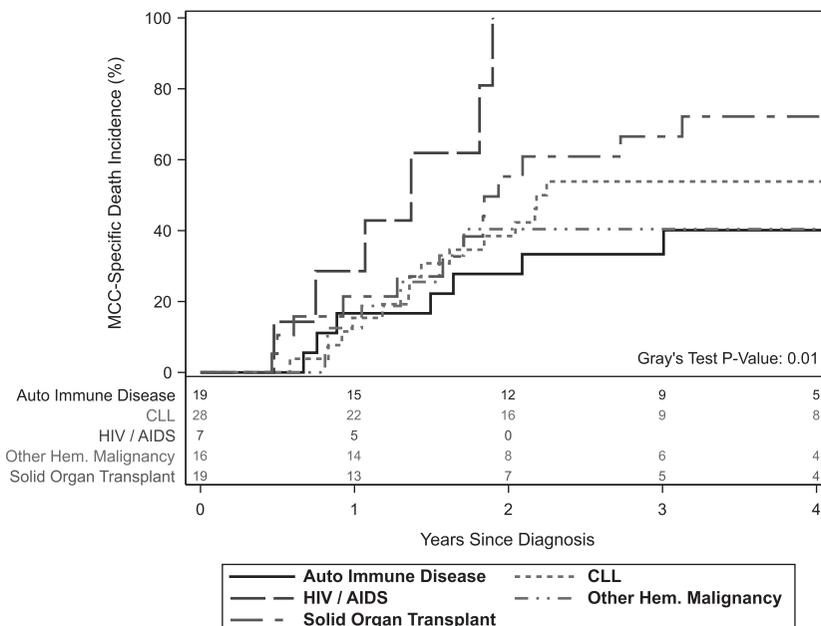


FIGURE 2. Cumulative incidence function of MCC-specific death among immunosuppressed patients by immunosuppression type. CLL indicates chronic lymphocytic leukemia; MCC, Merkel cell carcinoma.

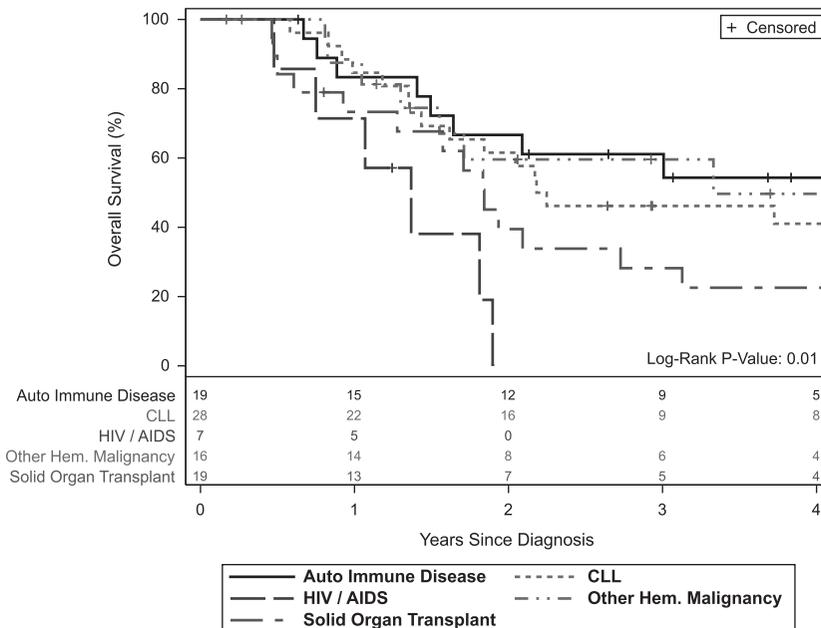


FIGURE 3. Kaplan-Meier plot of Merkel cell carcinoma overall survival among immunosuppressed patients by immunosuppression type.

DISCUSSION

To our knowledge, this is one of the largest reported cohorts of immunosuppressed MCC patients with comprehensive demographic, pathologic, treatment, and outcomes data. Although no significant differences in PFS were observed between immunosuppression types, significant differences in MSS and OS were observed, in which HIV/AIDS and SOT patients appeared to have worse survival outcomes, even after controlling for potentially confounding variables such as stage and age. In fact, immunosuppression type was the strongest predictor of OS.

Although all immunosuppressed patients with MCC are at high risk for recurrence and time to recurrence is short, the significant difference in MCC-specific death across immunosuppression types suggests that a proportion of MCC recurrences can be salvaged to prevent MCC-related death. Success of salvage treatment depends on site of relapse (local/regional versus distant), extent of initial

treatment, and availability of salvage therapies. MCC patients with HIV/AIDS had the worst MSS and OS, corresponding to the observation that the majority of first recurrences were distant and not curable. Although ~50% of patients with CLL, SOT, or AD had a local or regional first recurrence, MCC patients with SOT appeared to have worse MSS. It is unclear whether the worse MSS among SOT patients despite similar rates of local/regional first recurrence as CLL and AD patients is driven by fewer SOT patients being eligible for salvage treatment and/or lower rates of salvage efficacy. Regardless, the observation that 60% of MCC patients that experienced MCC death initially had nonmetastatic disease at first recurrence highlights the unmet need for novel therapy for patients with localized recurrent disease, who are at high risk of subsequent distant recurrence.

Although MCC patients in this study had significant comorbidities including chronic immunosuppression, MCC was still the most common cause of death. Most patients died of MCC (n = 48)

TABLE 3. Multivariate Regression Analysis for Predictors of PFS and OS

Variables	PFS			OS		
	Hazard Ratio	95% CI	P	Hazard Ratio	95% CI	P
Age	1.02	0.99-1.05	0.13	1.03	1.00-1.06	0.04
Enrollment lag time (mo)			0.02			0.24
< 6	Reference	—		Reference	—	
≥ 6	1.81	1.08-3.03		1.43	0.79-2.59	
Immunosuppression type			0.27			0.01
HIV/AIDS	2.95	0.98-8.87		8.45	2.43-29.41	
CLL	1.04	0.50-2.17		1.46	0.62-3.44	
Organ transplant	1.84	0.84-4.05		3.00	1.19-7.55	
Autoimmune disease	Reference	—		Reference	—	
Other hematologic malignancies	1.12	0.48-2.59		1.26	0.45-3.54	
Stage			0.24			0.69
I-II (local)	Reference	—		Reference	—	
III (nodal)	1.40	0.80-2.47		1.15	0.58-2.27	

Bold indicates significant P value.
 CI indicates confidence interval; CLL, chronic lymphocytic leukemia; HIV/AIDS indicates human immunodeficiency virus/acquired deficiency syndrome; OS, overall survival; PFS, progression-free survival.

rather than other causes ($n = 4$), which lead to very similar MSS and OS curves. This suggests that MCC-directed therapy should not be withheld due to the aggressive and malignant nature of MCC, particularly in an immunosuppressed host.

Our findings are consistent with other retrospective cohorts or population-based studies showing poor survival^{8–11,14,15} among immunosuppressed patients with MCC. Our results are also consistent with the findings that immunosuppression influences outcomes independent of stage at diagnosis.¹⁰ Although it is well documented that cutaneous malignancies occur with higher incidence among immunosuppressed patients^{20,21} and are associated with more aggressive behavior,^{22,23} to our knowledge, this is the first study to compare outcomes by type of immunosuppression among immunosuppressed patients with skin cancer.

The mechanisms contributing to altered outcomes among immunosuppressed groups are unknown, but may reflect altered response to therapies, ability to tolerate aggressive therapy, and/or ability of the host immune system to mount an antitumor response. The immune system is thought to play an important role in eradication and control of MCC. Indeed, MCC patients that present with regional disease of unknown primary (stage IIIB) have improved outcomes compared with other stage IIIB patients with known primary site,^{14,24} presumably in part due to an immune system that has successfully mounted an antitumor effect at the putative primary site.

Although studies have evaluated the impact of altering posttransplant immunosuppression on the incidence of skin cancers,^{25,26} the safety and efficacy of modulating an immunosuppressed host system after MCC diagnosis remains untested. Immune checkpoint inhibitors targeting programmed cell death protein (PD)-1 or PDL-1 are associated with 30% to 56% response rates among patients with metastatic MCC,^{27,28} but have only been prospectively tested among immune competent patients. On the basis of case reports of SOT patients with metastatic cutaneous squamous cell carcinoma or melanoma, tumor regression has been observed with pembrolizumab, nivolumab, and ipilimumab. Organ rejection was seen after anti-PD-1 therapy^{29,30} but not anti-CTLA-4 therapy.^{31–33} Another strategy includes altering immunosuppressive drugs in SOT patients. At least in melanoma patients with SOT, switching from inhibitors of calcineurin to inhibitors of mechanistic target of rapamycin was associated with reduced risk of transplant rejection and better survival outcomes.³⁴

The immune system may also mediate response to therapies including radiation. Local recurrence after palliative radiotherapy is higher among MCC patients with immunosuppression or exposure to chemotherapy versus immunocompetent MCC patients³⁵: 30% versus 9%. In addition, preliminary evidence suggests reduced efficacy with current, standard doses of curative-intent radiotherapy on PFS and local control among MCC patients with immunosuppression, compared with MCC patients with an intact immune system.¹⁹ Similar findings have been reported with palliative radiotherapy for CLL/small lymphocytic lymphoma (SLL) patients. Compared with other indolent non-Hodgkin lymphoma patients, CLL/SLL patients had lower response rate (odds ratio, 0.2; $P = 0.02$) and shorter time to further treatment for a local recurrence (hazard ratio, 3.63; $P = 0.01$) after radiotherapy.³⁶

Although hypothesis generating and limited by small numbers ($n = 7$), we found that HIV/AIDS patients had the worst disease outcomes compared with all other immune suppression types in this study. CD4 count > 200 has been prognostic for survival in HIV/AIDS patients with anal cancer.³⁷ However, in our cohort, 6 of 7 HIV/AIDS patients' CD4 counts were > 200 , and 5 of 7 had an undetectable HIV viral load at the time of MCC diagnosis. Thus, while CD4 count and viral load are commonly used to help define risk of illness from HIV/AIDS, these metrics may not wholly capture degree of

immunosuppression. Currently, there is no established biomarker for immune status in MCC. In a single retrospective study of 64 patients with MCC, absolute lymphocyte count $< 1.1 \text{ k/mm}^3$ was associated with significant differences in disease-free and OS,³⁸ although this remains to be validated.

This registry study is limited by its retrospective design and small numbers, although this is one of the largest reported immunosuppressed MCC cohorts with detailed treatment and pathology information. Details of immunosuppression (eg, changes in immunosuppressive drugs) were not available for all patients across time. Treatment received (surgery, radiation, chemotherapy) was likely biased by patient selection, although the relative proportion of those that underwent treatment was similar across immunosuppression types. Last, stage at diagnosis differed among the immunosuppression types, with HIV/AIDS and SOT patients having more advanced stage at diagnosis. Controlling for stage in our multivariate analysis, immunosuppression type remained a significant predictor for PFS and OS.

CONCLUSIONS

Despite competing comorbidities among immunosuppressed patients with MCC, most immunosuppressed MCC patients die from MCC. Time to recurrence is similar across all immunosuppressed MCC patients, but MCC-specific and OS are significantly different among immunosuppression types. This suggests that a subset of immunosuppressed patients with MCC may be successfully salvaged at the time of recurrence. Future work focusing on mechanisms of diminished immune responses by the type of immunosuppression could provide insight on therapeutic approaches for these MCC patients.

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