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Survival Analyses and Prognosis of Plasma Cell Myeloma and Plasmacytoma-Like Post-Transplant Lymphoproliferative Disorders

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Abstract

Background—Multiple myeloma/plasmacytoma-like post-transplant lymphoproliferative disorder (PTLD-MM) is a rare complication of solid organ transplant. Case series have shown variable outcomes and survival data in the modern era are lacking.

Methods—A cohort of 212 PTLD-MM patients was identified in the Scientific Registry of Transplant Recipients between 1999-2011. Overall survival (OS) was estimated using the Kaplan-Meier method and the effects of treatment and patient characteristics on OS evaluated with Cox proportional hazards models. OS in 185 PTLD-MM patients was compared with 4048 matched controls with multiple myeloma (SEER-MM) derived from SEER.

Results—Men comprised 71% of patients; extramedullary disease was noted in 58%. Novel therapeutic agents were used in 19% of patients (more commonly 2007-2011 versus 1999-2006 (P=0.01)), reduced immunosuppression in 55%, and chemotherapy in 32%. Median OS was 2.4 years, and improved in the later time period (aHR 0.64, P=0.05). Advanced age, creatinine>2, Caucasian race and use of OKT3 were associated with inferior OS in multivariable analysis. OS of PTLD-MM is significantly inferior to SEER-MM patients (aHR 1.6, p<0.001). Improvements in OS over time differed between PTLD-MM and SEER-MM. Median OS of patients diagnosed

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2000-2005 was shorter for PTLD-MM than SEER-MM patients (18 vs 47 months P<0.001). There was no difference among those diagnosed 2006-2010 (44 mo vs median not reached P=0.5) (interaction P=0.08).

Conclusions—Age at diagnosis, elevated creatinine, Caucasian race and OKT3 were associated with inferior survival in patients with PTLD-MM. Survival of PTLD-MM is inferior to SEER-MM, though significant improvements in survival have been documented.

Keywords

PTLD; Multiple Myeloma; Survival; Prognosis; Organ Transplantation

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous,[1] uncommon[2–6] complication of solid organ transplantation (SOT). Survival rates of PTLD patients reflect the compounded effects of malignancy and treatment in immunocompromised patients.[4,5,7–12] SOT patients have 1.8 – 3.8 times the risk of multiple myeloma and plasmacytoma, both recognized subtypes of PTLD,[1] compared with background populations.[13–15] Plasma cell myeloma and plasmacytoma-like PTLD (PTLD-MM) account for 3-6% of PTLD.[16–19]

Prognosis of PTLD-MM has been described in several case series and one registry study. Of the 55 cases reported as individual cases or small series, 41 reported survival, and 15 (37%) died. While responses to reduction in immunosuppression (RIS) were described, follow-up time was variable, ranging from 15 days to >10 years. [17–22] Prior to 2002, 160 PTLD-MM patients were identified in the USRDS prior to the current study. Overall survival was 65% at 5 years, and only 26% at 10 years. Survival of PTLD-MM was worse than other forms of PTLD. [23] Since that time, multiple myeloma survival rates have improved coincident with the approval, and rapid adoption, of the novel agents bortezomib, thalidomide and lenalidomide,[24,25] however their frequency of use for, and effect on the survival of, PTLD-MM has not been described.[18,22,26] Moreover, the difference between survival rates of PTLD-MM compared to myeloma patients in the modern era is unknown.

We therefore studied a large cohort of PTLD-MM patients diagnosed between 1999-2011 using prospectively collected data from the Scientific Registry of Transplant Recipients. We describe patient characteristics, treatment, survival rates, and factors associated with prognosis in PTLD-MM, and we compare temporal survival trends in PTLD-MM to that of myeloma.

Methods

Data Sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[27] The Health

Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. As of 1999, data on patients is collected by transplant centers at the time of solid organ transplant (SOT), 6 months and then on the anniversary of the SOT and entered into the online system UNet.

For comparison, patients with non-PTLD multiple myeloma (SEER-MM) were identified in the Surveillance and Epidemiology and End Results Program (SEER),[28] which provides demographic and survival information on all cancer patients in 18 geographic regions representative of the general United States population from 2000-2010.

Patient Identification

Patients were included in the PTLD-MM cohort if “Myeloma/Plasmacytoma” was recorded in the standardized diagnosis field or if a plasma cell dyscrasia was entered in a diagnosis related text field. Patients with additional primary malignancies, except for non-invasive non-melanoma skin cancers, were excluded, as were patients who did not have a PTLD subtype recorded. Patients with myeloma were identified in the SEER database using ICD-O-3 codes 9731-9732, and 9734. Only patients with survival times recorded were included.

Treatment Characteristics

Treatment was categorized as “reduced immunosuppression;” “cytotoxic” if patients ever received cytotoxic chemotherapy or interferon (1 patient); “novel,” if patients ever received thalidomide, lenalidomide or bortezomib; or “radiation therapy (XRT).” Treatment with novel agents was recorded in text fields only, rather than from the standardized chemotherapy list, so potential misclassification was assessed by comparing outcomes over time, using 2007 as a proxy for novel therapy use.

Ascertainment of Outcome

The SRTR determines the date of death by querying the organ procurement organizations, the individual transplant programs, and the Social Security Administration's death index on a monthly basis. Patients were presumed alive until the end of the follow up period (10/31/2011) unless a date of death was entered into the SRTR. PTLD-MM specific death was determined using death certificate derived causes of death. Any cause of death other than malignancy was considered non-PTLD-MM specific.

Statistical Methods

OS of patients with PTLD-MM was estimated using the Kaplan-Meier method. Cumulative incidence of PTLD-MM specific mortality, defined as time to death due to multiple myeloma, accounted for non-PTLD-MM related mortality as a competing risk using the methods of Fine and Gray.[29] Cox-proportional hazards regression models evaluated associations between baseline characteristics and OS. Missing data were assumed missing at random, and were multiply imputed for variables missing less than 50%.[30] Multivariable regression models were used to adjust for potential confounders and estimate adjusted hazard ratios (aHR). Creatinine, age, Karnofsky performance status (KPS) and date of diagnosis were included in all multivariable models. Additional variables were included in multivariable analysis where univariate P-values < 0.1.

To assess temporal trends in survival patients were divided into two cohorts based on diagnosis prior to, or after 1/1/2007. This cut point was chosen based on a published analysis of prescribing habits for myeloma patients.[25] Because patients diagnosed in 2007 and later could only be followed for a maximum of 4 years, all analyses adjusting for date of diagnosis censored patient follow-up at 4 years.

Statistical tests were considered significant if $P < 0.05$.

Comparison of PTLD-MM and SEER-MM

To compare the OS of patients with PTLD-MM and SEER-MM, patients were matched on age, gender, and year of diagnosis (2000-2010). One-to-many matching was utilized to maximize sample size. Race and ethnicity were recorded differently in the two databases, and were not included in the survival analysis. Kaplan Meier OS estimates were compared using the log rank test. Cox proportional hazards models adjusted for matching ratios, and stratified by match, compared the survival of PTLD-MM with SEER-MM. Temporal trends in survival were assessed by dividing the cohorts at the median year of diagnosis (2006), and comparing OS in the two time periods; 2007 was not used as a cutoff to ensure adequate follow up time in the later cohort. To determine if these trends differed between PTLD-MM and SEER-MM patients, diagnosis in the later time period was included in a multivariable model as an interaction term with diagnosis of PTLD-MM.

Sensitivity Analysis

Sensitivity analyses were performed to evaluate analytic assumptions and assess biases in the analysis. Survival analyses excluding patients identified in text fields, using traditional censoring techniques, and using only complete cases, were performed.

All statistical analyses were performed using R version 3.0.2,[31] (R Foundation for Statistical Computing, Vienna, Austria), and RStudio version 0.98.490,[32] (RStudio, Boston, MA). Matching was performed using the “MatchIt” package; multiple imputation was performed using the “mice” package; SEER data was analyzed using the “SEERaBomb” package; competing risk analysis was performed using the cmprsk package.

IRB exemption was obtained for this study under the determination of “Not Human Subjects Research,” based on the use of de-identified data.

Results

Patients

A total of 212 patients with PTLD-MM were identified (Table 1). Median time from SOT to PTLD was 4.8 years, with 18% developing the disease within 1 year, and 23% of patients being diagnosed more than 10 years after SOT. Extramedullary disease was common (58%); by contrast, allograft and CNS involvement were rare (3% each). EBV status of the tumor and of the patients were not reported in 79% and 62% of patients respectively. Thus these variables were not included in analyses.

Treatment

The majority of patients underwent reduction in immunosuppression (RIS). Treatment with novel agents was recorded in only 41 (19%) of patients (Table 1), and was rarely combined with chemotherapy (Figure 1). Patients diagnosed later were significantly more likely to have received novel agents (odds ratio (OR) per year 1.25, 95% CI 1.12 – 1.42); those diagnosed between 2007 – 2011 had 2.4 (95% CI 1.2 – 4.9) times the odds of receiving novel therapy compared with those diagnosed 1999-2006. The use of radiation decreased over time (Table 1) (OR 0.4, 95% CI 0.20 – 0.79).

Survival

A total of 134 (63%) patients died during the follow up period. Of these, 78 (43%) had myeloma or malignancy listed as a cause of death. The median OS was 2.4 years, and PTLD-MM specific mortality plateaued at 39% (Figure 2A-B).

Neither RIS nor XRT demonstrated an improvement in OS (HR (95% CI) 1.24 (0.86 – 1.78) and 1.28 (0.88 – 1.86) respectively); notably use of cytotoxic chemotherapy was associated with worse OS (HR 1.59 [1.12 – 2.25]). Controlling for age, KPS, creatinine and year of diagnosis did not affect the aHR (data not shown). Receipt of cytotoxic chemotherapy did not affect PTLD-MM specific mortality, but increased non-PTLD-MM specific mortality (3 year non-PTLD-MM specific mortality 31% (23% - 46%) vs. 15% (9% - 22%) respectively, P<0.05). No difference in OS or PTLD-MM specific mortality was demonstrated in patients receiving novel agents, compared to those who did not. A trend towards a decrease in non-PTLD-MM specific mortality was noted (3 year non-PTLD specific mortality 11% (3% -24%) vs 23% (16% - 30%), *P*=0.06).

Few patients were recorded as receiving novel agents in the SRTR. These drugs were only recorded in free text, while other treatments were selected from standardized lists. Therefore novel agent administration was potentially misclassified, likely under-reporting its use. To address this, diagnosis after 2007 was used as a proxy for widespread utilization of novel agents.[25] Diagnosis in the earlier cohort was associated with worse OS (median 22 months vs median not reached, *P*=0.01). PTLD-MM specific mortality in later cohort was not significantly improved (3 year PTLD-MM specific mortality 39% (31% - 48%) vs 27% (18% - 37%), *P*=0.18) (Figure 2C-D). A trend in non-PTLD-MM related mortality was noted (3 year mortality 24% (17% - 32%) vs 13% (6% - 23%), *P*=0.10).

In univariate analysis, age at diagnosis, male sex, Caucasian race, use of OKT3 as an immunosuppressive induction agent, increased creatinine, and extramedullary disease were associated with shortened OS (Table 2). In the multivariable analysis, sex was no longer associated with OS, while the association of extramedullary disease with OS was weakened. KPS, included as part of a pre-specified analytic plan, reached borderline significance (Table 2). Notably, after accounting for baseline characteristics, diagnosing PTLD-MM during the later time period remained associated with superior OS (adjusted HR (aHR) 0.64, 95% CI: 0.42 – 0.99).

Sensitivity Analyses

Sensitivity analyses accounting for patients recorded in text fields, using traditional censoring techniques rather than a “presumed-alive” analysis, and using disease specific rather than OS, showed largely stable effect estimates (Appendix Tables 2- 4). When using complete-case data, rather than multiply imputed data, race and the use of OKT3 were not associated with OS (aHR and 95% CI 1.1 (0.54 – 2.24) and 1.0 (0.24 – 4.39) respectively) (Appendix Table 3).

Comparison of PTLD-MM with SEER-MM

Overall, 25,931 SEER-MM patients were identified. These were older and less likely to be male than PTLD-MM patients. After matching, persistent imbalance in the overall cohort due to one-to-many matching was addressed in a weighted cox model (Appendix Table 5). Median OS in the SEER-MM cohort was not reached, compared with 29 months in the PTLD-MM cohort (log-rank P<0.001) corresponding to a HR of 1.63 (95% CI 1.34 – 1.99) (Appendix Table 1). At 4-year follow up, median OS for those patients diagnosed 2000 – 2005 was significantly worse in the PTLD-MM cohort (18 vs. 47 months respectively, log rank P<0.001), while in the later time period a survival discrepancy was not observed (44 mo vs. median not reached respectively, P=0.51) (Figure 3). A trend towards interaction between diagnosis and date (P=0.08), indicated greater improvement in PTLD survival over time.

Discussion

PTLD-MM is an infrequent complication of SOT, rendering prospective study challenging. We show use of registry data to describe outcomes in these patients is possible, and elucidates survival patterns relevant to clinical care. To the best of our knowledge, this represents the largest study to date of PTLD-MM conducted during the era of treatment with novel agents. Similar to prior reports, PTLD-MM patients were younger, predominantly male, and had frequent extramedullary involvement compared with SEER-MM patients, [13,15,23] reflecting, in part, the underlying SOT population.[13,33] While the median OS for the entire cohort was only 2.5 years, significant improvements in survival were seen over time. Furthermore, improvements in survival of PTLD-MM have outstripped that of SEER-MM, leading to similar survival times in the two diseases when diagnosed more recently. A plateau in the survival curve 10 years after diagnosis indicates that a proportion of patients are likely cured.

Associations Between Baseline Characteristics and Survival

In multivariable analysis, advanced age, Caucasian race, and elevated creatinine at diagnosis were associated with decreased OS, and we confirmed earlier findings that OKT3 use had an adverse effect on OS.[23] KPS <60% reached borderline statistical significance, and should be considered a poor prognostic factor.

Extramedullary disease was an adverse prognostic finding in the present study, retaining near-significance in the multivariable model. Two recent series of PTLD-MM[18,20] with a high proportion of extramedullary disease in both pediatric and adult SOT populations, and

two studies of plasmacytomas after SOT[17,19] reported survival rates superior to the current study. The reasons for these discrepant results are unclear, but reflect heterogeneity in PTLD-MM. Importantly, the inclusion of all U.S. SOT recipients in this analysis reduces the likelihood of selection bias.

The finding that Caucasians fared worse than other races is consistent with a population based analysis using SEER.[34] However, as information about race is recorded differently in the SRTR and SEER we did not compare outcomes in PTLD-MM and SEER-MM by race.

Treatment of PTLD-MM

Surprisingly, cytotoxic therapy adversely affected survival of PTLD-MM patients. Those with more advanced disease may have been more likely to receive chemotherapy, leading to confounding-by-indication. Adjusting for baseline characteristics did not alter this finding. Patients receiving chemotherapy were no less likely to die of PTLD-MM, but were more likely to die of other causes. In prior reports, RIS resulted in high response rates and in some patients, long term survival. In contrast, patients in the current study receiving RIS did not have an improvement in survival.

The use of novel agents increased over time. However, their overall use was recorded less frequent than expected. Misclassification and under-reporting are likely as novel therapies were not included in standardized selection lists. To account for this, year (2007) was employed as a proxy for novel therapy use, based on demonstrated uptake of these agents by physicians practicing in the US,[25] demonstrating improvement in OS over time. Though some patients in the earlier cohort received novel agents, this would presumably bias the analysis towards the null hypothesis, rather than towards statistical significance.

The temporal association between introduction of novel therapies and improved survival for myeloma has been documented.[24] However, the improvement in OS over time of PTLD-MM greatly exceeded that of SEER-MM in the current study. Several other trends in the care of PTLD-MM patients likely contributed to their improved OS over time. Awareness of the toxicities associated with treatment of PTLD increased during the study period,[8,9] with supportive care likely improving as a result. Post-SOT transplant care is likely to have improved over time as well, and may have influenced the survival rates of patients with PTLD-MM. Decreased non-PTLD-related mortality in the later time period supports both of these hypotheses, as well as the hypothesis that novel agents are better tolerated than cytotoxic therapies.

Study Strengths and Limitations

Observational studies are prone to biases and limitations. While the OPTN attempts to follow all SOT patients, loss to follow up is well documented.[3] The survival endpoint was ascertained rigorously using three independent methods, and is likely an accurate estimate unbiased by loss to follow up. Patients were included based on standardized data collection variables and text-fields. The inclusion of the latter allowed for a more robust sample size, but could have introduced selection bias. However, sensitivity analyses excluding these patients did not substantively change the results. Excluding the >30% of patients with missing data would result in a less generalizable and potentially biased study.[30] Multiple

imputation was thus employed to allow the use of the entire data set. When a complete-case analysis was run, effect estimates were similar for most variables, though race and OKT3 use lost statistical significance. That the complete-case findings in the current study are at odds with prior reports in myeloma and PTLD-MM for race,[34] and OKT3,[23] suggests that multiple imputation reduced bias.

The SRTR was designed to collect information most relevant to SOT teams. It captures treatment information annually, rather than at time of disease progression or time of therapy changing, and does not capture cytogenetic risk, or staging. How these factors interact with the patient and disease characteristics associated with OS in the current study remains unexplored.

Conclusions

Altogether, PTLD-MM patients have modest survival times, and patient characteristics easily ascertained at diagnosis, namely advanced age, Caucasian race, and elevated creatinine, are associated with shortened survival. Furthermore, PTLD-MM patients' survival rates remain inferior to SEER-MM patients', however outcomes have significantly improved in the modern era. This may be attributed to the integration of novel therapeutic agents. Given their tolerability,[22,26,35,36] treatment regimens based on novel, rather than cytotoxic, agents should be considered first line therapy for patients with PTLD-MM requiring systemic therapy.

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Aaron S Rosenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix: Tables

Appendix Table 1

Comparison of Overall Survival of PTLD-MM with SEER-MM in the Matched SRTR/SEER Cohort

	Univariate Model		Multivariable with Interaction	
	HR (95% CI)	***P*-value**	**aHR (95% CI)**	***P*-Value**
PTLD-MM	1.63 (1.34 – 1.99)	<0.001	1.89[††] (1.47 - 2.43)	<0.001
PTLD-MM [*] 2006[†]			0.70[*] (0.46 – 1.05)	0.08

Patients matched using one to-many matching; weights used to account for Various matching ratios; stratification used to account for matching

[†]Categorical date of diagnosis, using 1/1/2006 as a cut-point, reference category are those diagnosed 1/1/2000 – 12/31/2005

[††]aHR for PTLD-MM diagnosed in the earlier time period, accounting for the interaction with diagnosis date

[*]aHR for PTLD-MM diagnosed in the later time period, accounting for the interaction with diagnosis date: 1.36

Abbreviations: aHR: adjusted hazard ratio; HR: hazard ratio; PTLD-MM: plasma cell myeloma and plasmacytoma like PTLD

Appendix Table 2

Sensitivity Analysis: Effect of Different Patient Selection Techniques On Multivariable Models

	Multivariable Model 1: Primary Analysis (*N*=212)		Multivariable Model 2: Excluding Patients with Text Field Dx (*N*=123)	
Variable	**aHR (95% CI)**	***P*-value**	**aHR (95% CI)**	***P*-value**
Age (per 10 years)	1.27 (1.08 – 1.51)	0.005	1.29 (1.06 – 1.58)	0.01
Male	1.28 (0.81 – 2.03)	0.29	0.92 (0.51 – 1.65)	0.78
Caucasian	1.67 (1.00 – 2.78)	0.05	2.22 (1.06 – 4.66)	0.04
OKT3 Used for Induction	2.13 (1.06 – 4.26)	0.03	1.53 (0.68 – 3.43)	0.30
Creatinine>2 mg/dL	1.85 (1.06 – 3.21)	0.03	1.51 (0.82 – 2.79)	0.18
KPS 10-50[*]	1.82 (0.99 – 3.33)	0.05	1.93 (0.91 – 4.08)	0.09
Extramedullary Disease	1.47 (0.96 – 2.25)	0.07	1.98 (1.00 – 3.92)	0.05
Diagnosed 2007 - 2011[†]	0.64 (0.42 – 0.99)	0.05	0.69 (0.37 – 1.28)	0.24

[*]Reference KPS 60-100

[†]Reference group diagnosed 1999-2006

Abbreviations: aHR: adjusted hazard ratio; Dx: diagnosis; KPS: Karnofsky performance status

Appendix Table 3

Sensitivity Analysis: Effect of the Use of Traditional Censoring Techniques and Complete Case Analysis

	Multivariable Model 1: Primary Analysis (*N*=212)		Multivariable Model 4: Whole Cohort, Censoring at Last Follow up (*N*=212)		Multivariable Model 5: Complete Case Analysis, Presumed Alive (*N*=102)	
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age (per 10 years)	1.27 (1.08 – 1.51)	0.005	1.25 (1.05-1.50)	0.01	1.41 (1.10 - 1.83)	0.01

	Multivariable Model 1: Primary Analysis (*N*=212)		Multivariable Model 4: Whole Cohort, Censoring at Last Follow up (*N*=212)		Multivariable Model 5: Complete Case Analysis, Presumed Alive (*N*=102)	
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Male	1.28 (0.81 – 2.03)	0.29	1.21 (0.74-1.97)	0.45	1.19 (0.64 - 2.22)	0.59
Caucasian	1.67 (1.00 – 2.78)	0.05	1.67 (1.00-2.79)	0.05	1.10 (0.54 - 2.24)	0.79
OKT3 Used for Induction	2.13 (1.06 – 4.26)	0.03	1.88 (0.89-3.93)	0.10	1.03 (0.24 - 4.39)	0.97
Creatinine>2 mg/dL	1.85 (1.06 – 3.21)	0.03	2.04 (1.16-3.62)	0.02	2.16 (1.25 - 3.73)	0.01
KPS 10-50 *	1.82 (0.99 – 3.33)	0.05	2.05 (0.98-4.26)	0.05	2.17 (1.05 - 4.50)	0.04
Extramedullary Disease	1.47 (0.96 – 2.25)	0.07	1.43 (0.94-2.16)	0.09	1.78 (0.96 - 3.28)	0.07
Diagnosed 2007 -2011 †	0.64 (0.42 – 0.99)	0.05	0.82 (0.52-1.27)	0.37	0.49 (0.26 - 0.96)	0.04

*Reference KPS 60-100

†Reference category diagnosed 1999-2006

Abbreviations: aHR: adjusted hazard ratio; Dx: diagnosis; KPS: Karnofsky performance status

Appendix Table 4
Sensitivity Analysis: Disease Specific Survival

	Multivariable Model 1: Primary Analysis (*N*=212)		Multivariable Model 6: Disease Specific Survival (*N*=212)	
Variable	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age (per 10 years)	1.27 (1.08 – 1.51)	0.005	1.35 (1.09 - 1.68)	0.01
Male	1.28 (0.81 – 2.03)	0.29	0.89 (0.52 - 1.53)	0.68
Caucasian	1.67 (1.00 – 2.78)	0.05	1.78 (0.90 - 3.54)	0.10
OKT3 Used for Induction	2.13 (1.06 – 4.26)	0.03	1.83 (0.74 - 4.48)	0.19
Creatinine>2 mg/dL	1.85 (1.06 – 3.21)	0.03	1.63 (0.74 - 3.62)	0.21
KPS 10-50	1.82 (0.99 – 3.33)	0.05	2.03 (0.91 - 4.50)	0.08
Extramedullary Disease	1.47 (0.96 – 2.25)	0.07	1.85 (1.09 - 3.15)	0.02
Diagnosed 2007 - 2011 †	0.64 (0.42 – 0.99)	0.05	0.68 (0.39 - 1.18)	0.17

*Reference KPS 60-100

†Reference category diagnosed 1999-2006

Abbreviations: aHR: adjusted hazard ratio; Dx: diagnosis; KPS: Karnofsky performance status

Appendix Table 5
Characteristics of PTLD-MM and SEER-MM Patients

	Total Cohort		Matched Cohort*	
	PTLD-MM (SRTR) (*N*=192)	**SEER-MM (*N*=25931)**	**PTLD-MM (SRTR) (*N*=185)**	**SEER-MM (*N*=4048)**
Male	133 (69%)	14222 (55%)	131 (71%)	2960 (73%)
Age at Diagnosis	60 (52 - 78)	69 (59-78)	60 (53 – 67)	64 (58 – 69)

	Total Cohort		Matched Cohort*	
	PTLD-MM (SRTR) (*N*=192)	**SEER-MM (*N*=25931)**	**PTLD-MM (SRTR) (*N*=185)**	**SEER-MM (*N*=4048)**
Year of Diagnosis	2006 (2003-2008)	2005 (2002-2008)	2006 (2003 – 2008)	2006 (2004 – 2008)
Deceased	119 (62%)	15621 (60%)	117 (63%)	2095 (52%)

Continuous variables expressed as medians and interquartile ranges

*Matched on sex, age and year of diagnosis using one-to-many matching, which allows persistent imbalances in baseline characteristics, accounted for with weights in the Cox proportional hazards models

Abbreviations: PTLD-MM: plasma cell myeloma and plasmacytoma like PTLD; SEER-MM: Surveillance, Epidemiology and End Results Program multiple myeloma (non-solid organ transplant associated); SRTR: Scientific Registry of Transplant Recipients

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Clinical Practice Points

Multiple myeloma like post-transplant lymphoproliferative disorder (PTLD-MM) is a rare disorder accounting for only 3-6% of all PTLD cases. As such it has been incompletely studied and characterized. Treatment recommendations have been based on a small number of case reports/case series. Similarly, while the immunomodulatory agents (imids) and proteasome inhibitors (PIs) have revolutionized the treatment of multiple myeloma (MM), there is very little data about these agents use in PTLD or, more specifically, PTLD-MM. Thus the practicing clinicians and patients have little to guide them regarding prognosis or treatment.

The current study attempts to address these issues by analyzing prospectively collected data from a large solid organ transplant registry. Median overall survival (OS) of PTLD-MM was worse than has been previously reported, only 2.4 years. However, similar to multiple myeloma, great strides have been made over time: median OS of patients was not reached in those diagnosed in 2007, after imids and PIs were commonly used in clinical practice, while those diagnosed prior to 2007 was only 22 months. These effects were driven largely by decreased toxicity, with patients in the later cohort less likely to die of non-myeloma related causes. Finally, in a comparison with SEER matched controls, the rate of improvement in OS was more dramatic in PTLD-MM patients.

Taken in sum, the current study helps guide clinicians in their assessment and treatment of PTLD-MM patients by offering clear prognostic information and providing indirect evidence for treatment with imids and PIs.

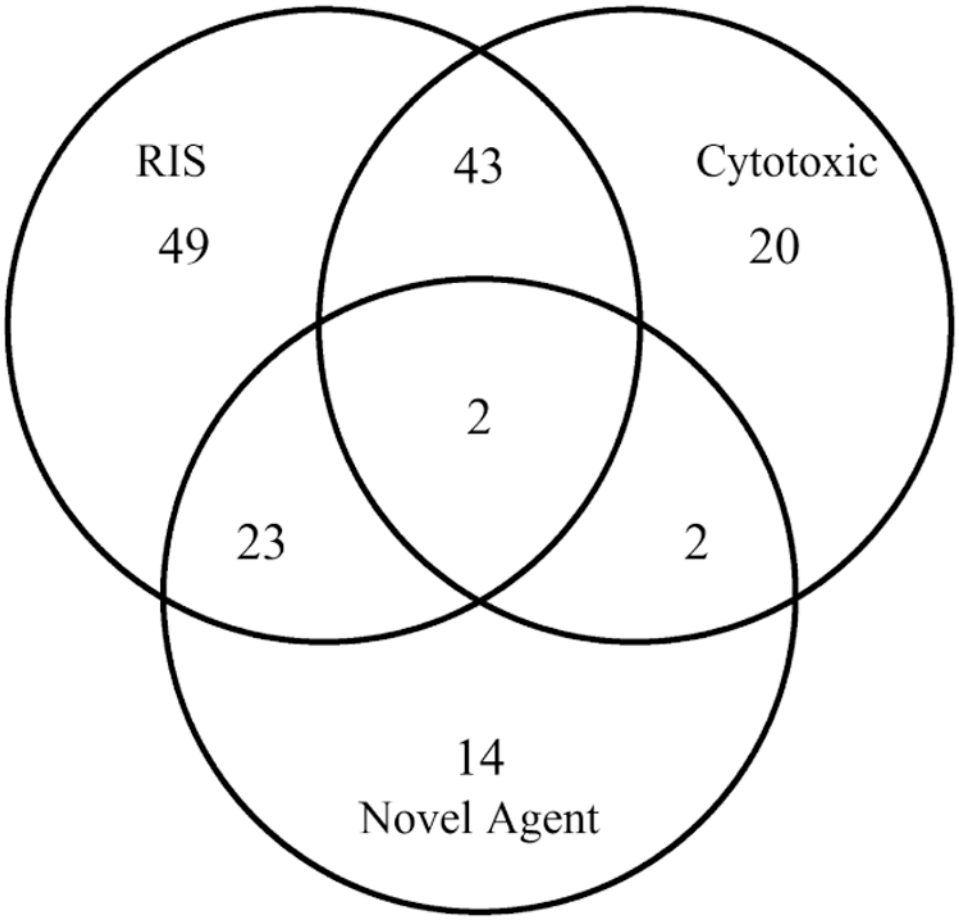

Figure 1. Recorded treatment characteristics of PTLD-MM patients

Novel agents include thalidomide, bortezomib or lenalidomide; cytotoxic therapy includes one patient who received interferon;

Abbreviations: RIS: Reduced Immunosuppression Therapy

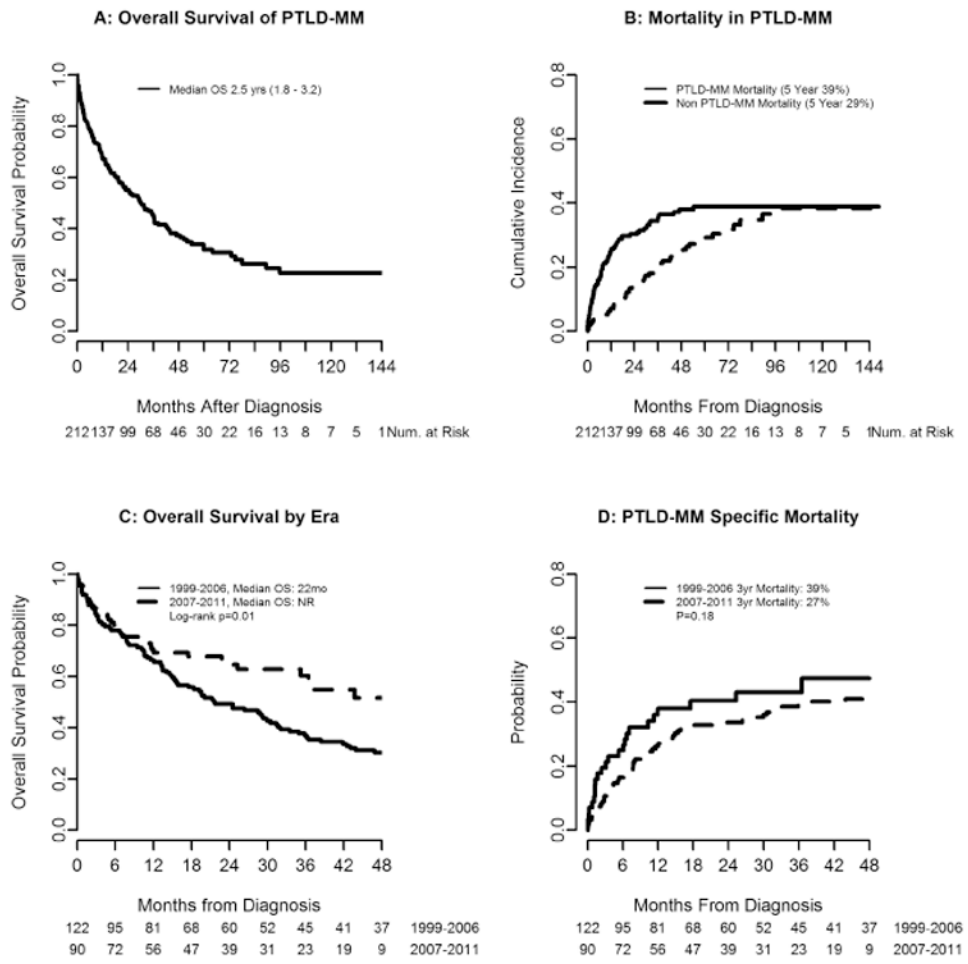

Figure 2.

A: Overall survival of the entire PTLD-MM cohort; ***B***: Cause specific mortality of PTLD-MM patients, as determined by death certificate data; ***C***: Overall survival of the PTLD-MM cohort comparing those diagnosed before 2007 to those diagnosed in 2007 and later; ***D***: Cumulative incidence of PTLD-MM specific mortality comparing those diagnosed before 2007 to those diagnosed in 2007 and later. Abbreviations: PTLD-MM: multiple myeloma and plasmacytoma like post-transplant lymphoproliferative disorder; OS: overall survival

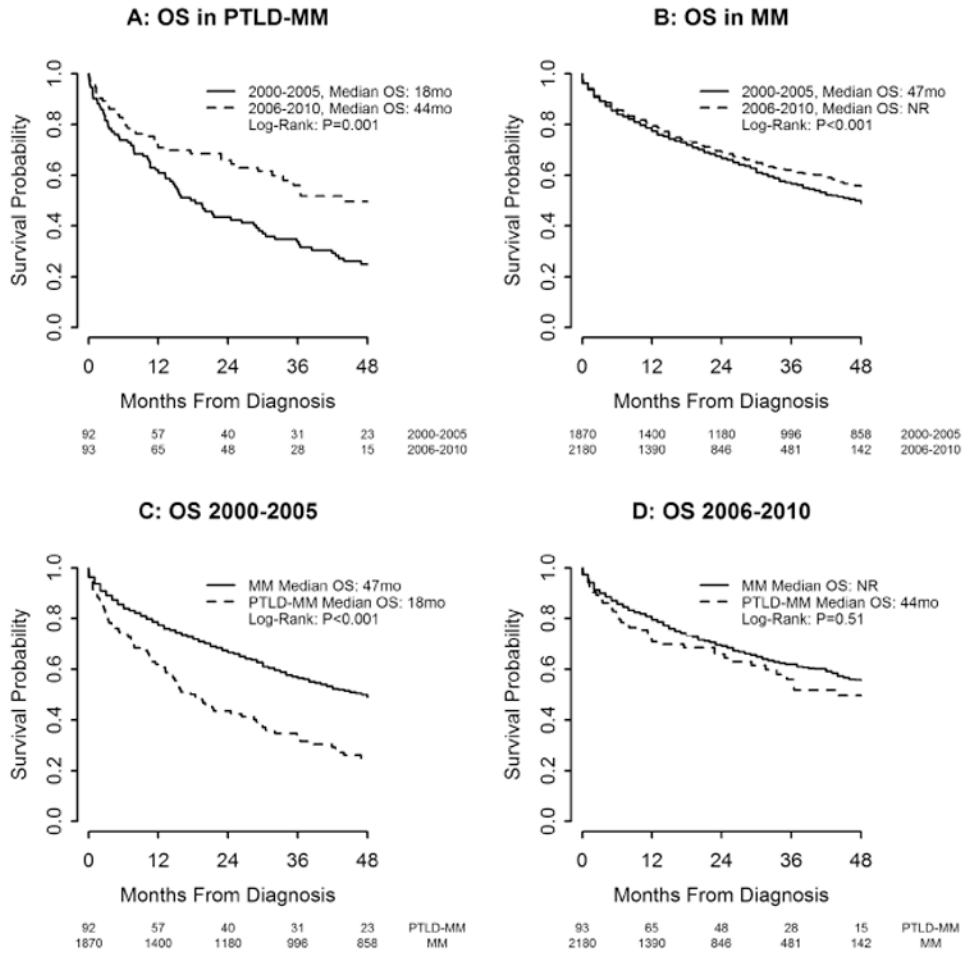

Figure 3. Legend: Survival of PTLD-MM and SEER-MM

Comparison of overall survival of PTLD-MM and SEER-MM patients in the earlier and later time periods. ***A***: OS of PTLD-MM in the matched cohort is significantly improved in the 2006-2010 (n=93, green dashed line) cohort compared to the 2000-2005 cohort (n=92, blue solid line) (log rank *P*=0.001). ***B***: OS for SEER-MM patients is modestly, but statistically significantly improved in the 2006-2010 cohort (n=2180, orange dashed) when compared to the earlier cohort (n=1870, red solid line) (log rank p<0.001). ***C***: In the earlier time period, OS of SEER-MM (n=1870, red solid line) is superior to that of PTLD-MM (n=92, blue dashed line) (log rank p<0.001), however ***D***: in the later cohort OS of SEER-MM (n=2181, orange solid line) and PTLD-MM (n=91, green dashed) is similar (P for interaction 0.02). Abbreviations: SEER-MM: Surveillance, Epidemiology and End Results Program multiple myeloma (non-solid organ transplant associated), derived from SEER18; PTLD-MM plasma cell myeloma and plasmacytoma like post-transplant lymphoproliferative disorders; NR: not reached; OS: overall survival

Table 1
Baseline Characteristics of Patients with PTLD-MM

Variable	Total Cohort (*N*=212)	1999-2006 (*N*= 122)	2007-2011 (*N*= 90)
Age	60 (52 - 67)	59 (50 - 66)	62 (54 - 68)
Male	149 (70%)	94 (77%)	55 (61%)
Caucasian *	164 (77%)	102 (84%)	62 (69%)
Kidney Transplant **	115 (54%)	61 (50%)	54 (60%)
Living Donor	48 (23%)	25 (20%)	23 (26%)
Induction Immunosuppression			
OKT3	15 (7%)	9 (7%)	6 (7%)
Anti-IL2 antibodies	44 (21%)	20 (16%)	24 (27%)
ATG/ALG	39 (18%)	16 (13%)	23 (26%)
None	59 (28%)	43 (35%)	16 (18%)
Creatinine gm/dL	1.6 (1.2 – 2.1)	1.7 (1.2 – 2.1)	1.5 (1.2 – 2.2)
unknown/missing	71 (33%)	49 (39%)	24 (26%)
Karnofsky Performance Status			
10-50	15 (7%)	6 (5%)	9 (10%)
60-70	18 (8%)	9 (7%)	9 (10%)
80-100	112 (53%)	78 (64%)	34 (38%)
unknown/missing	67 (32%)	29 (24%)	38 (42%)
Months from Transplant to PTLD	58 (19-105)	51 (14-101)	62 (22-120)
Extramedullary disease	124 (58%)	83 (68%)	41 (46%)
Prior Malignancy	13 (6%)	8 (10%)	5 (6%)
unknown/missing	53 (25%)	39 (32%)	14 (16%)
CMV IgG or IgM	76 (36%)	32 (26%)	43 (48%)
unknown/missing	95 (45%)	68 (55%)	27 (30%)
HCV at time of SOT	18 (8%)	11 (9%)	7 (8%)
unknown/missing	51 (24%)	38 (31%)	13 (14%)
HBV at time of SOT	9 (4%)	6 (5%)	3 (3%)
unknown/missing	31 (15%)	21 (17%)	10 (11%)
Treatment			
RIS	117 (55%)	76 (62%)	41 (46%)
unknown/missing	22 (10%)	3 (2%)	19 (21%)
Systemic therapy	127 (59%)	78 (63%)	49 (54%)
Cytotoxic Therapy (incl IFN)	67 (32%)	47 (39%)	20 (22%)
Novel Therapy	41 (19%)	18 (15%)	23 (26%)
Other	23 (11%)	13 (11%)	10 (11%)
unknown/missing	12 (6%)	2 (2%)	10 (11%)
Radiation Therapy	55 (26%)	42 (34%)	13 (14%)

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Variable	Total Cohort (*N*=212)	1999-2006 (*N*= 122)	2007-2011 (*N*= 90)
unknown/missing	19 (9%)	5 (4%)	14 (16%)
Non-biopsy Surgery	24 (11%)	19 (16%)	5 (6%)
unknown/missing	26 (12%)	6 (5%)	20 (22%)

Continuous variables expressed as median (interquartile ranges)
Abbreviations: ATG/ALG: Anti-thymocyte globulin; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HBV: hepatitis B virus; HCV: Hepatitis C virus; IFN: interferon; RIS: Reduced immunosuppression; SOT: Solid organ transplant;

*Black 29 (14%), Hispanic/Latino (6%), Asian 5 (2%), American India/Alaskan Native 3 (1%)

**Heart 47 (22%), Liver 35 (17%), Lung 4 (2%), Pancreas 1, Intestine 1, Multiple 9 (4%)

Table 2
Associations Between Baseline Characteristics and Overall Survival *N=212*

	Univariate		Multivariable Including Date	
Variable	**HR (95%CI)**	***P*-value**	**aHR (95%CI)**	***P*-value**
Age (per 10 years)	1.26 (1.08 - 1.47)	0.004	1.27 (1.08 – 1.51)	0.005
Male	1.69 (1.10 – 2.62)	0.02	1.28 (0.81 – 2.03)	0.29
Caucasian	1.85 (1.13 – 3.01)	0.01	1.67 (1.00 – 2.78)	0.05
Kidney Transplant	0.91 (0.64 – 1.30)	0.61		
Living Donor	0.79 (0.51 - 1.230	0.31		
Induction Immunosuppression: OKT3 *	2.01 (1.08 – 3.74)	0.03	2.13 (1.06 – 4.26)	0.03
Creatinine> 2 mg/dL	1.71 (1.07 – 2.71)	0.03	1.85 (1.06 – 3.21)	0.03
Performance Status 10-50 **	1.62 (0.88 – 2.97)	0.12	1.82 (0.99 – 3.33)	0.05
Years from Transplant to PTLD	0.99 (0.95 – 1.03)	0.54		
Extramedullary Disease	1.47 (1.01 – 2.14)	0.04	1.47 (0.96 – 2.25)	0.07
Prior Malignancy	1.47 (0.72 – 3.01)	0.28		
CMV †	1.01 (0.60 – 1.70)ar	0.98		
HCV †	1.56 (0.89 – 2.70	0.11		
HBV †	0.64 (0.30 – 1.48)	0.30		
Diagnosed 2007-2011 ††	0.60 (0.41 – 0.90)	0.01	0.64 (0.42 – 0.99)	0.05

*Compared to anti-IL2 antibodies, ATG and none; no other regimens statistically significant

**Compared to KPS 60-100 as reference category

†CMV measured at time of SOT and during follow up; HCV and HBV measured at time of SOT only

††Reference group: patients diagnosed 1999-2006

Abbreviations: aHR: adjusted Hazard Ratio, ALG: anti-lymphocyte globulin, ATG: Anti-thymocyte globulin, CMV: cytomegalovirus, HBV: hepatitis B virus, HCV: hepatitis C virus, HR: Hazard Ratio, KPS: Karnofsky performance status; SOT: Solid Organ Transplant