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Allogeneic Haematopoietic Cell Transplantation Impacts on Outcomes of Mantle Cell Lymphoma with *TP53* Alterations

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Summary

TP53 alterations portend extremely poor prognosis in patients with mantle cell lymphoma treated with standard treatment modalities. We reviewed outcomes of 42 patients with available *TP53* status who had received a reduced-intensity or non-myeloablative allogeneic haematopoietic cell transplant at our institution. We demonstrated a 2-year overall survival and progression-free survival of 78% (95% confidence interval [CI] 60–88) and 61% (95% CI 43–75), respectively. The 2-year cumulative incidences of relapse and non-relapse mortality were 19% and 20%, respectively. Importantly, there is no significant difference among patients with and without *TP53* alterations, suggesting for the first time a beneficial treatment modality for these high-risk patients.

Keywords

allogeneic hematopoietic cell transplant; mantle cell lymphoma; *TP53*

Mantle cell lymphoma (MCL) is largely considered an incurable non-Hodgkin lymphoma characterized by the chromosomal translocation t(11;14), resulting in overexpression of cell cycle protein cyclin D1. MCL predominantly affects older adults and has an aggressive

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Author contributions

RJL, CH and CSS designed the study and wrote the manuscript. RJL, PDH and CSS analysed the data. KSR contributed essential data management. All the remaining authors (JNB, SAG, AAJ, HRC, EBP, MAP) contributed data to the study and every author critically appraised and approved the final version of the paper.

Competing interests

The authors have no competing interests.

clinical course with a pattern of relapsing or refractory disease (Mussetti *et al*, 2015a). The molecular pathogenesis of MCL involves stepwise disease progression driven by oncogenic cyclin D1 and transcription factor SOX11, and by subsequent alterations in tumour suppressor genes, such as *TP53* (Jares *et al*, 2012). *TP53* plays a pivotal role in DNA damage response and regulation of apoptosis, and its alterations seem to occur later in lymphomagenesis, contributing to the development of highly aggressive blastoid or leukaemic variants of MCL (Jares *et al*, 2012). *TP53* alterations can be detected cytogenetically (chromosome 17p deletion), molecularly (oncogenic mutations) or immunohistochemically (mutant TP53 protein overexpression). They all confer a dismal prognosis for overall survival (OS) and progression-free survival (PFS) (Halldórsdóttir *et al*, 2011; Nordström *et al*, 2014).

Several recent studies have evaluated the effect of different therapies on *TP53*-altered MCL. Upfront cytarabine-containing induction chemoimmunotherapy followed by high-dose chemotherapy consolidation with autologous stem cell transplantation (ASCT) did not overcome the dismal prognosis associated with either *TP53* deletion or oncogenic mutations in younger MCL patients (Eskelund *et al*, 2017). Similarly, combining chemoimmunotherapy with lenalidomide has not been shown to be effective in *TP53*-altered MCL patients, although adding ibrutinib to lenalidomide has shown encouraging activity in these patients (Jerkeman *et al*, 2018). We hypothesized that allogeneic haematopoietic cell transplantation (allo-HCT) may overcome the poor prognosis of *TP53* alteration, given its allo-immune mechanism of action (graft-versus-lymphoma). Here we examined the impact of *TP53* alterations in MCL patients who had received a reduced intensity or nonmyeloablative conditioning (RIC/NMA) allo-HCT at our institution.

Patients and Methods

This retrospective study included 42 consecutive patients who received a RIC/NMA allo-HCT at our institution for the treatment of MCL between 1999 and 2018. A waiver of authorization for this retrospective review was obtained from the Memorial Sloan Kettering Institutional Review and Privacy Board. Standard institution eligibility criteria, procedure and supportive care for transplant applied. Transplant outcomes of 17 of these 42 patients were reported previously (Mussetti *et al*, 2015b). Eight of these 17 patients were also included in a previously reported phase II trial of peri-transplant rituximab in patients with B-cell lymphoid malignancies (Sauter *et al*, 2014a).

Pathological diagnosis for MCL was confirmed for each patient by a Memorial Sloan Kettering Cancer Center (MSKCC) pathologist. TP53 protein was scored as low/negative expression (<30% tumour nuclei strongly positive) or high expression (≥30% tumour nuclei strongly positive), and Ki67 scored as a percentage of positive tumour nuclei, according to published immunohistochemical methods (Nordström *et al*, 2014). The Ki67 cut-off value of 30% was chosen based on Hoster *et al* (2016). Chromosome 17p deletion was detected using standard fluorescence in-situ hybridization (FISH) technique. Oncogenic *TP53* mutations were detected using next-generation sequencing technology developed and validated at MSKCC (Cheng *et al*, 2015).

Data analyses were performed using a cut-off date of 31 May 2018. The association between clinical and transplant characteristics with *TP53* status were assessed using the chi-squared, Fisher's exact and Wilcoxon rank sum tests as appropriate. OS and PFS were estimated using the Kaplan-Meier method. The cumulative incidence of relapse, non-relapse mortality (NRM), and acute and chronic graft-versus-host disease (GVHD) was estimated using the cumulative incidence method for competing risks. Death, relapse, and relapse or death were considered competing risks for relapse, NRM, and GVHD respectively. Cox Proportional Hazard regression models were used to assess univariate associations with clinical and transplant characteristics, with cause-specific Cox models used for relapse and non-relapse mortality. All statistical analyses were performed with R software, v3.4.4 (R Core Development Team, Vienna, Austria).

Results and Discussion

From our institutional transplant database, we identified 57 MCL patients who had received an allo-HCT. For this analysis, we excluded patients who received a myeloablative conditioning (n=4); did not have *TP53* information available (n=11); or received an alemtuzumab-containing regimen, due to their poor outcomes (n=6) (Sauter *et al*, 2014b). A total of 42 patients were included in the final analysis (Table I). The cohort consisted of predominantly males (n=39, 93%) with a median age of 61 years at the time of transplant (range, 34–74 years). RIC/NMA conditioning regimens included various dosage combinations of cyclophosphamide, fludarabine and total body irradiation, with or without peri-transplant rituximab; or various dosage combinations of fludarabine and melphalan. The majority of patients had 10/10 human leucocyte antigen-matched donors (n=31, 74%), followed by single allele mismatched donor (n=5), double cord units (n=3) and haploidentical donors (n=3). One-third of patients had received *in-vivo* T-cell depletion with anti-thymocyte globulin (ATG). Nineteen patients had *TP53* alterations including chromosome 17p deletion (n=3), oncogenic mutations (n=7) and high *TP53* protein overexpression by immunohistochemical stains (n=9). There were no statistically significant differences in demographic, clinical or transplant characteristics among patients with and without *TP53* alterations (Table I).

The median follow-up for survivors was 24 months (range 4–119). The two-year estimated OS PFS was 78% (95% confidence interval [CI] 60–88) and 61% (95% CI 43–75), respectively (Figure 1A). The estimated two-year cumulative incidence of relapse and NRM was 19% (95% CI 8–33) and 20% (95% CI 8–35), respectively (Figure 1B). The estimated cumulative incidences of grade II-IV acute GVHD was 43% at 180 days (95% CI 28–57), and any chronic GVHD was 33% at 2 years (95% CI 17–49). There was no statistically significant difference in OS (Figure 1C), and cumulative incidence of relapse (Figure 1D) between patients with and without *TP53* alterations. Additional analysis using 50% as the cut-off for high *TP53* protein overexpression by immunohistochemical stains did not change the overall similarity in survival and relapse among patients with or without *TP53* alterations (data not shown). In univariate analyses, we found that only Ki67 >30% was a significant predictor of PFS (hazard ratio [HR] 4.1, 95% CI 1.1–15.5, $p=0.024$), and that only Karnofsky Performance Status (KPS) 80 was a significant predictor of OS (HR 4.9, 95% CI 1.4–17, $p=0.01$). The univariate analyses are summarized in Table SI.

Herein we report, for the first time that, allo-HCT using RIC/NMA regimens could overcome the negative prognostic impact of *TP53* alterations in a relatively older cohort of MCL patients (median age 61 years). In our retrospective cohort, 2-year OS and PFS were 78% and 61%, respectively. These results are comparable with published reports on allo-HCT in MCL patients (Mussetti *et al*, 2015a; Robinson *et al*, 2018).

Several potential mechanisms could account for our observation. As a tumour suppressor gene, *TP53* is the guardian of the genome and controls apoptosis, cell cycle progression and intracellular metabolism in response to various cellular stresses. It is one of the most frequently altered genes in human cancer, including most B-cell malignancies, resulting in poor survival. Given that *TP53* alterations act downstream of most cellular growth signalling and DNA-damage repair pathways, it is not surprising that they lead to resistance to conventional high dose chemotherapy ASCT and pathway inhibitors. Allo-HCT, on the other hand, provides novel, non-apoptotic mechanisms of tumour cell killing through alloreactive cytotoxic and Natural Killer T-cells (Martínez-Lostao *et al*, 2015). In addition, *TP53* alterations are known to induce an immune-suppressive tumour microenvironment and a blunted host tumour immune response (Uehara & Tanaka, 2018), thus an allo-HCT has the potential to replace the dysfunctional host immune system. Finally, cytotoxic chemotherapy and alloreactivity may add synergistically to overcome resistance generated from *TP53* alterations. Similar mechanisms of action may operate in *TP53*-altered chronic lymphocytic leukaemia where allo-HCT has also been shown to be effective (Gribben, 2018).

Our study has several limitations. Firstly, it is a retrospective, single institution study with small sample size and thus is subject to potential patient selection bias, especially in a tertiary referral centre. For example, most patients had chemosensitive disease prior to transplant. In addition, *TP53* status was analysed by different methods and there could be differences in clinical outcomes among these alterations. Secondly, the heterogeneity in disease course, lines of therapy, type of donors, ibrutinib use prior to transplant and various RIC/NMA conditioning regimens employed limited the critical appraisal of the optimal donor or preparative regimen. Finally, the low event rate did not allow in-depth examination of multivariate risk factors contributing to OS and relapse.

Despite these limitations, our results add to the growing literature on the effectiveness of RIC/NMA allo-HCT for MCL patients. Most importantly, the observation that *TP53* status did not affect survival and relapse suggest that RIC/NMA allo-HCT should be considered for MCL patients with *TP53* alterations, as long-term survival is possible in these patients, possibly even earlier in the disease course. The use of RIC/NMA allo-HCT as the consolidative approach in first remission for select high-risk *TP53*-altered patients warrants prospective investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Risk Table

Outcome	0-month	12-month	24-month	36-month	48-month
OS	42	31	19	13	12
PFS	42	26	15	10	10

Risk Table

Outcome	0-month	12-month	24-month	36-month	48-month
NRM/Relapse	42	26	15	10	10

(C)

Risk Table

<i>TP53</i> Status	0-month	12-month	24-month	36-month	48-month
Negative	23	18	10	7	7
Positive	19	13	9	6	5

(D)

Risk Table

<i>TP53</i> Status	0-month	12-month	24-month	36-month	48-month
Negative	23	16	8	5	5
Positive	19	10	7	5	5

Figure 1.

(A) Kaplan-Meier (KM) Plots of overall survival (solid line) and progression-free survival (dotted line) of the entire cohort. (B) Cumulative incidences of relapse (dotted line) and non-relapse mortality (solid line). (C) KM Plots of overall survival for patients with (dotted line) or without (solid line) *TP53* alteration. (D) Cumulative incidences of relapse in patient with (dotted line) or without (solid line) *TP53* alteration

Table I.

Patient Characteristics.

Characteristic	Total (N=42)	TP53 – (N=23)	TP53 + (N=19)	<i>p</i> value
Age, years; median (range)	61.2 (33.9–73.7)	61.2 (33.9–71.3)	61.2 (49.1–73.7)	0.570
Female sex, N (%)	3 (7)	2 (9)	1 (5)	>0.999
KPS 80, N (%)	12 (29)	5 (22)	7 (37)	0.462
HCT-CI, N (%)				0.481
0	9 (21)	5 (22)	4 (21)	
1–2	16 (38)	7 (30)	9 (47)	
3	17 (40)	11 (48)	6 (32)	
Ki67 >30%, N (%)	17 (40)	8 (42)	9 (60)	0.490
MIPI Risk Index, N (%)				0.914
Low risk	16 (38)	8 (35)	8 (42)	
Intermediate risk	20 (48)	11 (48)	9 (47)	
High risk	6 (14)	4 (17)	2 (11)	
Lines of prior therapy; median (range)	3 (1–6)	3 (1–6)	3 (1–6)	0.874
SD/PR at HCT, N (%)	2 (5)	1 (4)	1 (5)	>0.999
Prior ASCT, N (%)	27 (64)	14 (61)	13 (68)	0.853
First-line consolidation, N (%)	8 (19)	5 (22)	3 (16)	0.709
Ibrutinib pre-transplant, N (%)	17 (40)	9 (39)	8 (42)	>0.999
ATG use, N (%)	14 (33)	8 (35)	6 (32)	>0.999
Matched donor, N (%)	31 (74)	19 (83)	12 (63)	0.180
HCT prior to 2011, N (%)	10 (24)	6 (26)	4 (21)	>0.999

ASCT, autologous stem cell transplant; ATG, anti-thymocyte globulin; HCT-CI, haematopoietic cell transplant-comorbidity index; KPS, Karnofsky performance scale; MIPI, Mantle cell lymphoma International Prognostic Index; N, number; PR, partial remission; SD, stable disease; *TP53* –, *TP53* normal; *TP53* +, *TP53* altered.