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Trends in pre- and post-transplant therapies with first autologous hematopoietic cell transplantation among patients with multiple myeloma in the United States, 2004–2014

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To The Editor

Multiple myeloma (MM), the second most common hematologic malignancy in adults with an estimated ~30,000 new cases in the United States each year(1) has seen remarkable improvements in survival since the turn of the century.(2) These improvements are in a large part related to the availability and use of novel therapies such as proteasome inhibitors and immunomodulatory drugs as well as novel treatment paradigms such as upfront autologous hematopoietic cell transplantation (AHCT), post-transplant consolidation and/or maintenance therapies within the last decade. Upfront AHCT remains the standard-of-care in transplant-eligible patients.(3, 4) We analyzed trends in pre- and post-transplant therapies and survival outcomes among patients undergoing AHCT for MM in the United States (US) using the Center for International Blood and Marrow Transplant Research (CIBMTR) database. The purpose of this analysis was to show real-world trends in patients, induction chemotherapies and post-transplant treatments in the US during a period which has seen several paradigm changes in multiple myeloma management.

This study was approved by the Institutional Review Board of the Medical College of Wisconsin. First single AHCT in the US (n=37,705) using high dose melphalan for MM of consented patients and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), 2004–2014 were included and a representative subset (n=5,077) with detailed research level data were studied in sub-analyses. Data on use of individual

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chemotherapies for induction and post-transplant therapies were obtained (vincristine/adriamycin/dexamethasone, VAD; thalidomide, T; lenalidomide, R; bortezomib, V; cyclophosphamide, C; dexamethasone, D and the combinations TD, RD, VD, VTD, VCD and VRD). Trends were studies in 3 time cohorts based on year of transplant: 2004–2007, 2008/09, and 2010–14. These periods were determined based on meaningful changes that occurred with induction and maintenance treatments, 2004–2007 (VAD and TD induction, no V/R maintenance), 2008–2009 (doublets and triplets with V and/or R) and 2010–2014 (novel triplet and R maintenance). During this period, the CIBMTR captured 60–80% of all AHCT activity for MM in the US. Demographic, disease-related and treatment-related data were analyzed. Post-transplant therapy was defined as immediate post-AHCT therapy used in the absence of relapse and/or progression of MM; in this setting it captures both consolidation and maintenance. Data on post-transplant therapies were available after 2008. Kaplan-Meier method was used to conduct survival analysis; the median progression free (PFS) and overall (OS) survival analysis were compared in the years 2004–2007, 2008–2009, 2010–2014. Multivariate analysis was performed using Cox proportional hazards method. The year of transplant group was the main effect; age, Karnofsky performance score (KPS), advanced stage at diagnosis (ISS III and/or DSS III), time from diagnosis to transplant, number of chemotherapy regimens prior to transplant, disease status prior to transplant and melphalan conditioning dose were also factored in the model. Both pre-transplant and post-transplant therapies were not further analyzed in the models as these variables were confounded by close correlation with the 'year of transplant' variable. Further, post-transplant therapies were only available during a portion of this study.

Table 1 shows baseline demographic data for the 5077 patients (2004–2007, N =2,034, 2008–2009, N=1156, 2010–2014, N=1,887). The median follow-up of survivors was 68 months (1–135). The median age at transplant remained stable over the studied period at 59 years; with 15% of patients being 65–70 years and 7% of patients being >70 years at transplant. The proportion of patients >65 years did not increase over this time period. More patients after 2008 were transplanted with a KPS < 90%. A strong trend was seen for fewer patients undergoing transplant in advanced stage over this time period (p-value < 0.0001). This has never been described or studied in MM before. Next, a trend toward fewer patients undergoing transplant after 1 year of diagnosis over this period and in concordance to this finding, more patients underwent transplant after 1 line of chemotherapy after 2010. This is in keeping with practice changing clinical trials supporting the use of AHCT in the upfront setting during this period.(5, 6) Figure 1A shows the various induction regimen trends over the period. The use of VAD/similar regimens which were the most commonly used induction regimen as recently as the 2004/05 period have all but phased out, and replaced by RVD in the 2012/14 period, followed closely by VCD and VD. The use of RD which peaked in 2008–2009 has been declining as an induction agent. In the US, T-based doublet/triplet use is very infrequent after 2009. Nearly 79% of patients are treated with triplet induction regimens in the 2010–2014 period. Among patients with creatinine < 2 mg/dl, more patients are receiving Mel 200 mg/m^2 over time while the reverse trend is occurring among patients with creatinine ≥ 2 mg/dl where more patients are receiving reduced melphalan 140 mg/m^2 (Supplemental table 1). Planned post-transplant treatments (consolidation and/or maintenance) at day 100 after AHCT were more frequent after 2010 (Figure 1B) with

lenalidomide being the most frequent maintenance agent. The frequency of maintenance utilization did not go up significantly from 2010 to 2014, and only 51% of patients received post-transplant therapies during this period. Similar findings were seen with post-transplant therapy use at 6 months (Figure 1C). This finding is a little surprising because despite evidence from several randomized clinical trials supporting the use of post-transplant maintenance during this study period,(3, 7, 8) only half of patients were reported to be on post-transplant therapy in our study. It is possible that after 2014, these numbers have continued to increase and may be more evident in the coming years.

The median PFS was 19 (17–21), 29 (26–31) and 41 (38–45) months for 2004–2007, 2008–2009 and 2010–2014 respectively. The median OS was 75 (72–80), 75 (72–78) and not reached for 2004–2007, 2008–2009 and 2010–2014 respectively. Univariate survival data showed a steady improvement in PFS over the study period with 3-year PFS improving from 31 (28–33)% in 2004–2007 to 38 (35–41)% in 2008–2009 to 53 (50–56)% in 2010–2014 (p-value < 0.001). Similarly, the 3-year OS also showed improvement over the time period; 75 (74–77)% in 2004–2007 to 77 (74–79)% in 2008–2009, to 80 (78–83)% in 2010–2014 (p-value 0.001). Among the patients who died, myeloma remained the most common cause of death: 2004–2007, 72%; 2008/09, 76%; 2010–2014, 78%.

On multivariate analysis, PFS was improved by year of transplant group (reference 2004–2007) with 2008–2009 showing HR 0.8 (95% CI, 0.7, 0.9, p-value < 0.001) and 2010–2014 HR 0.6 (0.5, 0.6, p < 0.001). Other factors associated with worse PFS included KPS < 90 HR 1.1 (1.0-1.2), p 0.01, advanced stage at diagnosis HR 1.2 (1.1, 1.3, p < 0.0001), use of >1 line of chemotherapy HR 1.3 (1.2, 1.4 p < 0.0001) and a disease status of < CR at the time of transplant; PR 1.2 (1.1, 1.4, p 0.004), < PR 1.4 (1.2, 1.6, p 0.0002). For OS, year of transplant was no longer significant when adjusted for age, KPS, advanced stage at diagnosis, lines of chemotherapy, disease status at transplant and time from diagnosis to transplant. (Supplementary table 2 shows complete multivariate analysis). Survival figures are shown in Supplemental Figure 1A (3–year PFS) and Figure 1B (3–year OS).

The likely impact on PFS improvement after 2010 may be both changes in induction therapies as well as post-transplant therapies and it is impossible to tease out the individual impacts of either factor using this dataset. The finding of a change of OS improvement from significant gains on univariate analysis to no difference in multivariate analysis warrants further discussion, in particular in the context of the trend that fewer patients had advanced stage at diagnosis over time that was seen during this period. Advanced stage significantly impacted OS in the current analysis. This leads us to speculate whether there is an introduction of a lead-time bias in MM transplant studies in the current era. Of note, our survival analysis only extends to 3 years, and given the excellent 3-year OS even in 2004–2007, further gains may be hard to improve upon. Longer follow up may well show the impact of improved post-relapse therapies on OS.

In conclusion, our trends analysis capturing the majority of US MM AHCT activity over a 11 year period in a contemporaneous era shows that the outcomes of upfront AHCT recipients for MM have improved over 2004–2014 at a steady pace over time with a substantial improvement in the most recent time cohort. On multivariate analysis, PFS

improvements have been significant in recent years while OS has remained unchanged over this period when adjusted for age, stage at diagnosis, time from diagnosis to transplant and disease status at transplant. VRD has become the most common pre-transplant induction regimen after 2010. Only, half of patients are placed on post-transplant treatment at day 100 after AHCT, with lenalidomide as the most frequently used agent. Counterintuitively, we did not see an increase in the use of maintenance treatment in the most recent period. Despite these impressive gains in the field, progression of MM remains the most frequent cause of death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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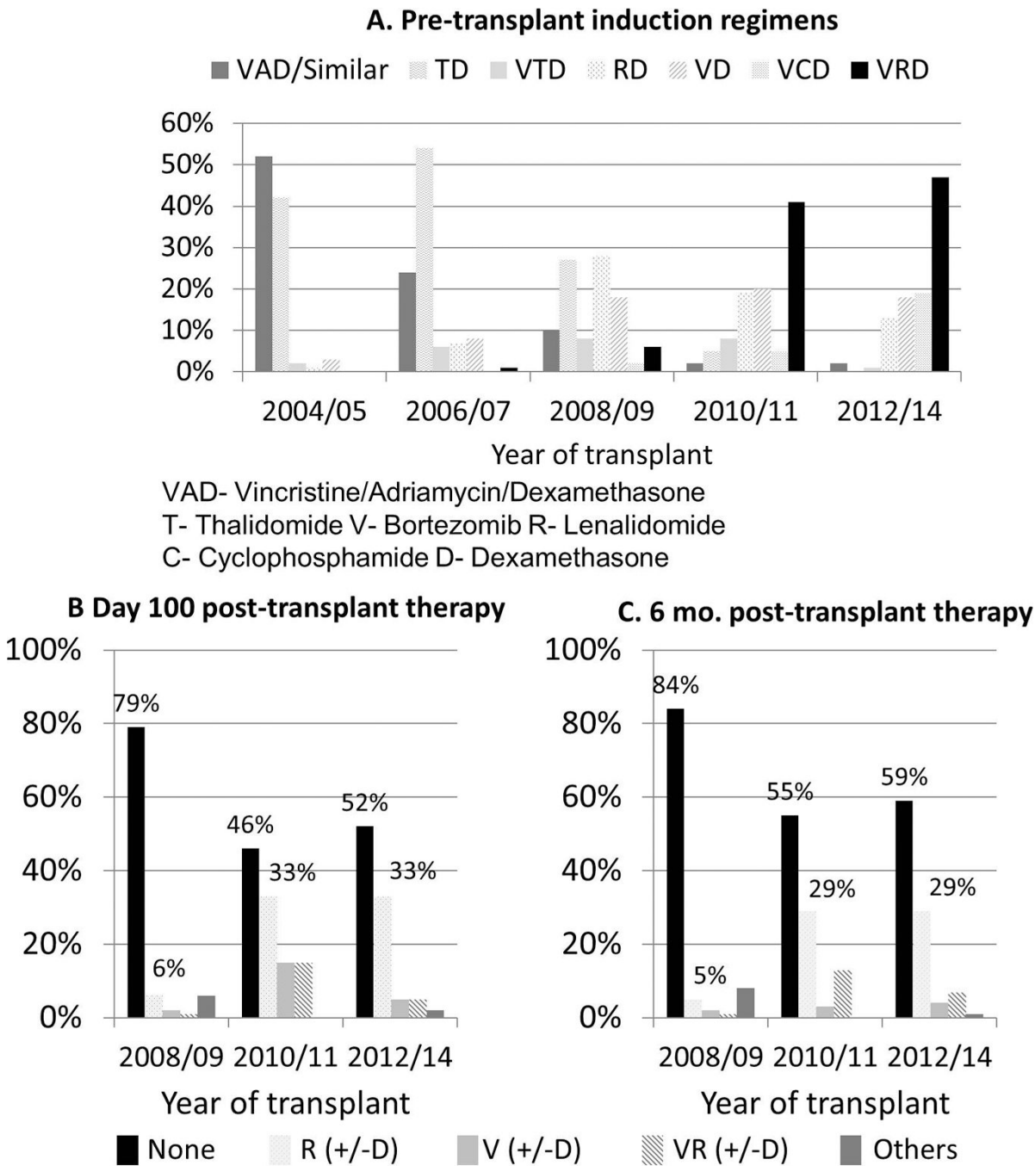

Figure 1.

Trends in pre-transplant induction (Figure 1A), day 100 post-transplant therapy (Figure 1B), 6 month post-transplant therapy (Figure 1C).

Table 1

Baseline characteristics of patients

Variable	2004–2007	2008–2009	2010–2014
Number of patients	2034	1156	1887
Number of centers	111	92	111
Age at transplant, years			
Median(range)	58 (23–79)	59 (23–78)	59 (20–82)
<45	221 (11)	93 (8)	173 (9)
45–64	1417 (70)	784 (68)	1281 (68)
65–70	268 (13)	201 (17)	292 (15)
>70	128 (6)	78 (7)	141 (7)
Gender			
Male	1213 (60)	680 (59)	1071 (57)
Female	820 (40)	476 (41)	816 (43)
Missing	1 (<1)	0	0
Race			
White	1615 (79)	910 (79)	1306 (69)
Black	334 (16)	198 (17)	489 (26)
Missing	85 (4)	48 (4)	92 (5)
Karnofsky Performance Score			
>= 90%	1117 (55)	619 (54)	1075 (57)
< 90%	719 (35)	477 (41)	788 (42)
Missing	198 (10)	60 (5)	24 (1)
Serum Creatinine at transplant (mg/dl)			
<2	1924 (95)	1087 (94)	1804 (96)
>= 2	101 (5)	63 (5)	76 (4)
Missing	9 (<1)	6 (<1)	7 (<1)
Advanced Stage at diagnosis *			
Yes	762 (37)	358 (31)	538 (29)
No	1166 (57)	673 (58)	1158 (61)
Missing	106 (5)	125 (11)	191 (10)
Melphalan dose mg/m^2			
140	387 (19)	174 (15)	218 (12)
200	1647 (81)	982 (85)	1669 (88)
Lines of chemotherapy			
1	1239 (61)	728 (63)	1436 (76)
2	573 (28)	285 (25)	313 (17)
3/>	222 (11)	143 (12)	138 (7)
Chemotherapy			

Variable	2004–2007	2008–2009	2010–2014
VAD/similar	480 (24)	28 (2)	7 (<1)
TD	953 (47)	177 (15)	8 (<1)
VTD	201 (10)	157 (14)	69 (4)
RD	89 (4)	318 (28)	181 (10)
VD	33 (2)	109 (9)	191 (10)
VCD	245 (12)	143 (12)	329 (17)
VRD	30 (1)	223 (19)	1099 (58)
Others	2 (<1)	1 (<1)	3 (<1)
Unknown	1 (<1)	0	0
Disease status at transplant			
CR	25 (1)	170 (15)	310 (16)
PR	1716 (84)	831 (72)	1409 (75)
MR/SD	264 (13)	90 (8)	119 (6)
Relapse/Progression	29 (1)	65 (6)	49 (3)
Time from diagnosis to transplant, months			
Median(range)	8 (3–146)	9 (2–295)	7 (1–210)
< 6 months	492 (24)	245 (21)	650 (34)
6 – 12 months	1095 (54)	556 (48)	853 (45)
12 – 24 months	286 (14)	216 (19)	219 (12)
> 24 months	161 (8)	139 (12)	165 (9)
Median follow up of survivors, months (range)	98 (2–135)	72 (3–91)	24 (1–66)

*Advanced stage defined as ISS or DSS III