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Association Between Autologous Stem Cell Transplant and Survival Among Californians With Multiple Myeloma

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Abstract

Background: Autologous hematopoietic stem cell transplant (aHSCT) is an efficacious treatment for newly diagnosed multiple myeloma patients. However, as rapid advances have resulted in other highly efficacious and less intensive therapies, the role of aHSCT has been questioned.
Methods: We utilized population-based data to identify 13 494 newly diagnosed patients younger than age 80 years between 1998 and 2012. Patient characteristics of aHSCT and non-aHSCT groups were balanced using inverse probability weighting of a propensity score predicting aHSCT use. Multivariable models adjusted for baseline comorbidities, demographics, and socioeconomic status estimated the adjusted hazard ratio (aHR) and 95% confidence intervals (CIs) of death.
Results: Twenty point eight percent (2807) of patients underwent aHSCT, and this rate increased over time from 15.4% in 1998–2002 to 23.9% in 2008–2012. aHSCT was utilized among 37.6% and 11.5% of patients younger than age 60 years and 60 to 79 years, respectively. The median time to aHSCT was 9.4 months, and 89% of all aHSCTs occurred within two years of diagnosis. The median overall survival from time of aHSCT was 72.9 months (95% confidence interval [CI] = 68 to 78). Autologous HSCT at any time was associated with improved survival (aHR = 0.83, 95% CI = 0.75 to 0.92). Among aHSCT recipients, transplant more than 12 months after diagnosis (vs ≤12 months) was associated with worse survival (aHR = 1.33, 95% CI = 1.16 to 1.51). The positive effect of aHSCT on overall survival was similar across study time periods and age groups.
Conclusion: In the era of highly efficacious induction therapies, aHSCT remained infrequently used but continued to be associated with improved survival for multiple myeloma patients and should be considered for newly diagnosed patients.

Autologous hematopoietic stem cell transplant (aHSCT) has been considered a standard treatment approach for fit patients younger than age 65 years with multiple myeloma since overall survival (OS) benefits were demonstrated in 1996 (1). Over the last two decades, four new classes of highly efficacious agents have been approved for the treatment of multiple myeloma, resulting in prolonged survival of patients (2–4). Given the improved outcomes with newer agents, the continued use of aHSCT has been questioned (5,6).

Two recently reported European trials demonstrated improved OS when aHSCT was incorporated into initial therapy (7,8). Early results of the EMN02/HO95 trial, which randomized newly diagnosed multiple myeloma patients to consolidative chemotherapy or aHSCT, have demonstrated a progression-free survival (PFS) benefit, with an OS benefit in higher-risk patients (9,10). The IFM2009 study demonstrated improvement in PFS, but no difference in OS, when aHSCT was used as part of initial therapy (11). Thus, while aHSCT appears to improve PFS, its effect on OS remains uncertain in the modern treatment era.

It is well appreciated that patients enrolled in clinical trials differ from the overall patient population (12). This difference may be particularly pronounced for multiple myeloma patients (13). Population-based studies can provide important information on the effectiveness of aHSCT outside of the clinical trials setting. Therefore, to determine the effect of aHSCT on survival, we utilized a population-based cohort of newly diagnosed multiple myeloma patients in California from 1998 to 2012, a period

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in which immunomodulatory agents and proteasome inhibitors became widely used (14).

Methods

Data Source and Patients

This retrospective observational cohort study utilized linked data between the California Cancer Registry (CCR) and California Patient Discharge Database (PDD) and Ambulatory Surgery (AS) Database. The CCR is a statewide population-based cancer surveillance system collecting cancer incidence and mortality information since 1988; it captures more than 98% of all cancer diagnoses in the state. From the CCR, we obtained date of diagnosis, initial course of treatment, and patient demographics, including race/ethnicity, sex, age, residence, marital status, neighborhood socioeconomic status (15), and insurance type at time of diagnosis (16). The PDD captures all discharges from nonfederal hospitals in California since 1991. Beginning in 2005, the Ambulatory Surgery (AS) database, including all hospital-associated AS facilities, has also been mandated. The databases were linked at the patient level using the record linkage number (RLN), an encrypted form of social security number. The RLN allows serial linking of multiple hospitalization records over time. Patients who did not have an RLN (11%) or were only reported by the Department of Veterans Affairs (which does not send data to the PDD or AS) were excluded. Both PDD and AS include up to 25 diagnoses and up to 21 procedures associated with each hospitalization, coded using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), in the PDD and Current Procedural Terminology (CPT) in the AS. Each procedure code has an associated date.

First primary multiple myeloma patients were identified in the CCR using ICD-O-3 histology code 9732 (17). Because no patient older than age 80 years underwent aHSCT, we limited our analysis to patients age 18–79 years at diagnosis, similar to prior analyses (18,19). All cases were pathologically confirmed. Autopsy and death certificate diagnoses were excluded.

This study was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the University of California, Davis, Institutional Review Boards.

Only first aHSCT use was examined, and it was considered present if it was identified in either the CCR, PDD, or AS using codes included in Supplementary Table 1 (available online). Comorbidities were captured up to two years prior to the multiple myeloma diagnosis date. They were identified using the Elixhauser index, excluding cancer (20), and categorized as no admissions in PDD within the two prior years (and therefore could not be ascertained), zero comorbidities, one or two comorbidities, and three or more comorbidities. Socioeconomic status (SES) is measured at the neighborhood level by the CCR and divided into quintiles (15).

Statistical Analysis

Matched Kaplan-Meier curves compared survival from the time of aHSCT to death from all causes using the log-rank test. Patients with aHSCT were matched to up to two non-aHSCT patients on age (+/− 3 years), year of diagnosis (+/− 2 years), sex, race/ethnicity, SES, comorbidities, and follow-up time using greedy matching. To account for immortal time bias, each non-aHSCT patient had to be alive at the time of the matched transplant, and survival times were estimated from this point forward. The median follow-up time for the entire study population was calculated using the reverse Kaplan-Meier method (21,22).

Multivariable Cox proportional hazard regression models were used to estimate the effect of aHSCT on the adjusted hazard ratio (aHR) and 95% confidence intervals for death (OS) and disease-specific mortality (disease-specific survival [DSS]), after accounting for baseline characteristics. To account for immortal time bias (23–25), aHSCT was included as a time-dependent covariate. Propensity score methodology was utilized to mitigate the potential confounding by indication seen in multivariable models in retrospective studies. Logistic regression was used to create a propensity score for aHSCT (Supplementary Table 2, available online). Propensity matching, using nearest-neighbor matching, and inverse probability weighting (IPW) were then used in the Cox proportional hazards regression models for survival (26). The standardized mean differences (SMDs) in baseline covariates between the aHSCT and no-aHSCT groups were used to determine the effectiveness of the propensity score adjustment (Supplementary Figure 1, available online). An SMD of less than 10% is considered optimal. The IPW models provided the best balancing of covariates and were considered the primary analyses. Propensity score–matched and traditional regression models were considered sensitivity analyses.

New developments in multiple myeloma treatment during the study period may have altered the potential benefit of aHSCT (2,3,14). To assess whether the effect of aHSCT differed by treatment era, we included era of diagnosis and aHSCT use in an interaction term in the models. In a secondary analysis, we determined the effect of early aHSCT (<12 months after diagnosis) vs late aHSCT (≥12 months after diagnosis) among patients who underwent aHSCT. For all regression analyses, the proportional hazard assumption was assessed using Schoenfeld residuals (27). Initial chemotherapy use and comorbidities violated the proportional hazard assumption and were included as stratification variables.

All analysis was performed using SAS version 9.4. All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

There were 13 494 patients with multiple myeloma younger than age 80 years, of whom 2807 (20.8%) underwent aHSCT (Table 1, Figure 1). Compared with the non-aHSCT group, patients undergoing aHSCT were younger (median age at diagnosis = 56 compared with 67 years), had fewer comorbidities, and were less likely to have been hospitalized during the two years preceding diagnosis. Only 89 (2.0%) patients age 70 to 79 years at diagnosis underwent aHSCT, while 913 (21.2%) age 60 to 69 years and 1805 (37.6%) younger than age 60 years underwent aHSCT. The median time to aHSCT was 9.4 months, with 65.7% (n = 1843) of patients undergoing aHSCT within 12 months, and 88.7% (n = 2486) within 24 months of diagnosis. The median times from diagnosis to aHSCT were 9.2, 10.0, and 8.9 months for patients diagnosed in 1998–2002, 2003–2007, and 2008–2012, respectively. Among those patients undergoing transplant 12 months or more after diagnosis, the median time to transplant was 18.3 months. Over time, the use of aHSCT increased from 15.4% in 1998–2002 to 23.9% in 2008–2012. The median follow-up time was 98.5 months for the entire cohort, 100.3 months for the non-aHSCT group, and 95.5 months in the aHSCT group.

After matching on baseline characteristics, and time from diagnosis to transplant, the median OS after aHSCT was 72.9

Table 1. Baseline characteristics of California multiple myeloma patients, 1998–2012

Variables	All No. (%)	Any transplant No. (%)	No transplant No. (%)	P*
All	13 494 (100)	2807 (100)	10 687 (100)	
Sex				
Male	7425 (55)	1629 (58)	5796 (54.2)	<.001
Female	6069 (45)	1178 (42)	4891 (45.8)	<.001
Race/ethnicity				
NH white	7483 (55.5)	1624 (57.9)	5859 (54.8)	.004
African American	1859 (13.8)	313 (11.2)	1546 (14.5)	<.001
Hispanic	2751 (20.4)	595 (21.2)	2156 (20.2)	.23
Asian/PI	1232 (9.1)	260 (9.3)	972 (9.1)	.78
Other/unknown	169 (1.3)	15 (0.5)	154 (1.4)	<.001
Age at diagnosis, y				
<40	247 (1.8)	111 (4)	136 (1.3)	<.001
40–49	1280 (9.5)	542 (19.3)	738 (6.9)	<.001
50–59	3277 (24.3)	1152 (41)	2125 (19.9)	<.001
60–69	4303 (31.9)	913 (32.5)	3390 (31.7)	.42
70–79	4387 (32.5)	89 (3.2)	4298 (40.2)	<.001
Year of diagnosis				
1998–2002	4017 (29.8)	618 (22)	3399 (31.8)	<.001
2003–2007	4554 (33.7)	1013 (36.1)	3541 (33.1)	.003
2008–2012	4923 (36.5)	1176 (41.9)	3747 (35.1)	<.001
1st course of treatment				
Chemotherapy	9573 (70.9)	2626 (93.6)	6947 (65)	<.001
No chemotherapy	3691 (27.4)	174 (6.2)	3517 (32.9)	<.001
Unknown chemotherapy	230 (1.7)	7 (0.2)	223 (2.1)	<.001
Radiation	3130 (23.2)	804 (28.6)	2326 (21.8)	<.001
No radiation	10 358 (76.8)	2003 71 (4)	8355 (78.2)	<.001
Unknown radiation	6 (0)		6 (0.1)	.21
Neighborhood SES status				
1–lowest	2049 (15.2)	322 (11.5)	1727 (16.2)	<.001
2	2500 (18.5)	434 (15.5)	2066 (19.3)	<.001
3	2781 (20.6)	590 (21)	2191 (20.5)	.55
4	3056 (22.6)	718 (25.6)	2338 (21.9)	<.001
5–highest	3108 (23)	743)	2365 (22.1)	<.001
Residence at time of diagnosis				
Urban	12 941 (95.9)	2694 96)	10 247 (95.9)	.83
Rural	553 (4.1)	113 (4)	440 (4.1)	.83
Insurance coverage				
No insurance/self-pay	237 (1.8)	20 (0.7)	217 (2)	<.001
Private insurance	6802 (50.4)	1907 (67.9)	4895 (45.8)	<.001
Medicaid/government	1265 (9.4)	294 (10.5)	971 (9.1)	.03
Medicare	4765 (35.3)	532 (19)	4233 (39.6)	<.001
Unknown insurance	425 (3.1)	54 (1.9)	371 (3.5)	<.001
Marital status				
Never married	1898 (14.1)	369 (13.1)	1529 (14.3)	.12
Married	8250 (61.1)	1996 (71.1)	6254 (58.5)	<.001
Previously married	2716 (20.1)	369 (13.1)	2347 (22)	<.001
Unknown marital status	630 (4.7)	73 (2.6)	557 (5.2)	<.001
Comorbidities (2 y prior)				
No admissions in prior 2 y	5338 (39.6)	1378 (49.1)	3960 (37.1)	<.001
0	1135 (8.4)	351 (12.5)	784 (7.3)	<.001
1–2	2921 (21.6)	634 (22.6)	2287 (21.4)	.17
3+	4100 (30.4)	444 (15.8)	3656 (34.2)	<.001
Vital status as of 12/31/2012				
Overall death	8900 (66)	1173)	7727 (72.3)	<.001
Multiple myeloma death	6686 (49.5)	994 (35.4)	5692 (53.3)	<.001

*All comparisons were tested using bivariate chi-square testing, and all statistical tests were two-sided. NH = Non-Hispanic; PI = Pacific Islander; SES = socioeconomic.

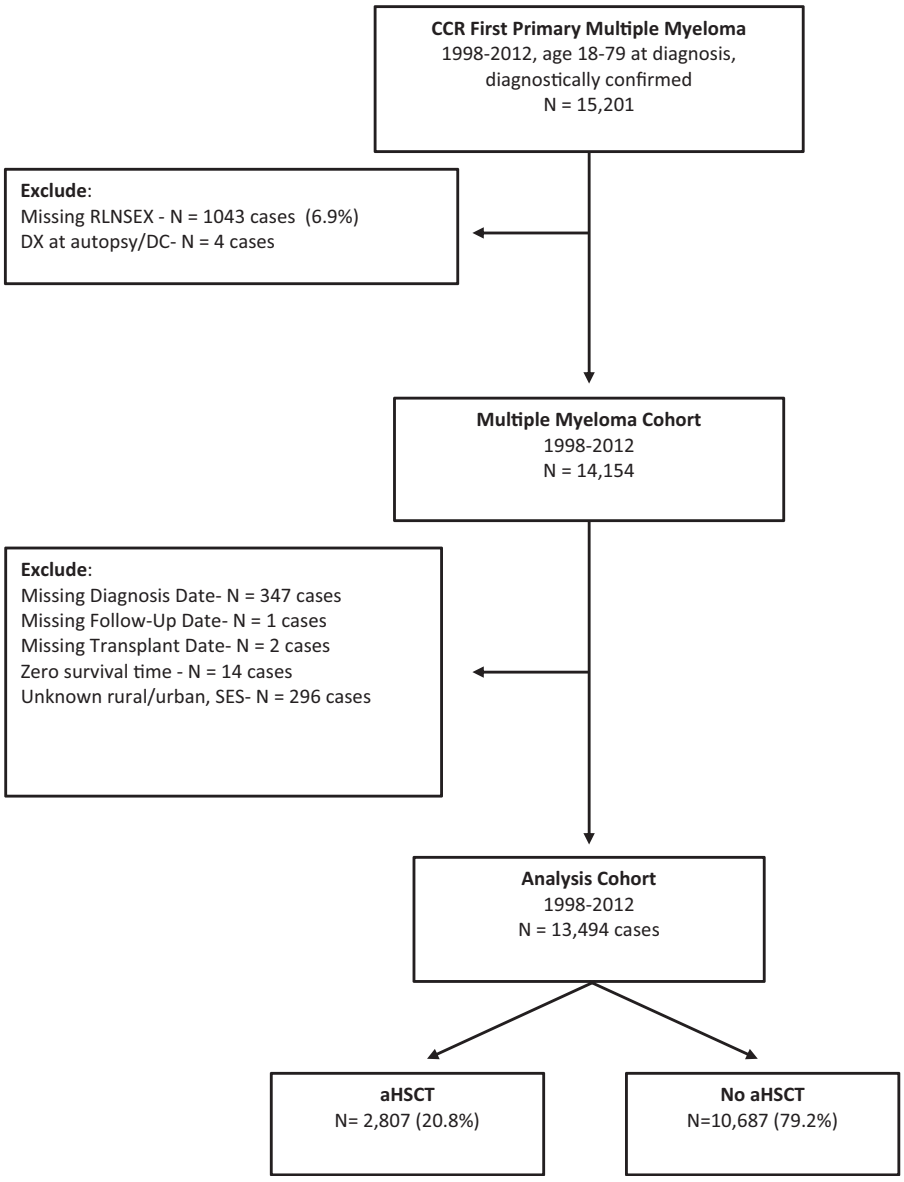

Figure 1. Diagram of patient identification and selection. aHSCT = autologous hematopoietic stem cell transplant; CCR = California Cancer Registry; DX = diagnosis; RLNSEX = record linkage number; SES = neighborhood socioeconomic status.

(95% confidence interval [CI] = 68.3 to 78.1) months among those who underwent aHSCT. Controls, who were matched to an aHSCT patient on time from diagnosis to transplant, had a median OS from the matched aHSCT time of 47.6 (95% CI = 45.0 to 50.9) months ($P < .001$) (Figure 2).

In the IPW analysis, aHSCT was associated with an improvement in OS from time of diagnosis, with a 17.0% decrease in the hazard of death (aHR = 0.83, 95% CI = 0.75 to 0.92) (Table 2). This improvement in survival was greater using propensity score–matched and traditional regression models (Table 2). Disease-specific survival was not statistically significantly different between aHSCT and non-aHSCT groups, with an adjusted hazard ratio of 0.91 (95% CI = 0.81 to 1.03). However, in both the propensity score–matched and traditional regression models, there was an association between aHSCT use and improved DSS similar in magnitude to what was seen with OS (Table 2).

The association between aHSCT and OS was similar over time in the IPW analysis ($P_{interaction} = .29$). However, in both the propensity score–matched and traditional regression models, the association between aHSCT use and improved survival increased over time ($P_{interaction} < .001$ for both). (Table 3) The effect of aHSCT on OS was similar across all age groups ($P_{interaction} = .75$, .52, and .67 for IPW, propensity score–matched, and traditional regression models, respectively).

We then examined aHSCT patients and compared those who underwent aHSCT less than 12 months after diagnosis (early aHSCT) and those who underwent aHSCT 12 or more months after diagnosis (late aHSCT). Non-Hispanic whites were more likely to get early aHSCT, while African Americans were more likely to get late aHSCT. Early aHSCT was utilized more commonly during the later study period (2008–2012) compared with the early study periods, though this finding was not statistically significant in the multivariable propensity model (Supplementary Tables 3 and 4, available online). After accounting for baseline demographics in the IPW model (Supplementary Figure 2, available online), late aHSCT was associated with a 33.0% increase in the hazard of death

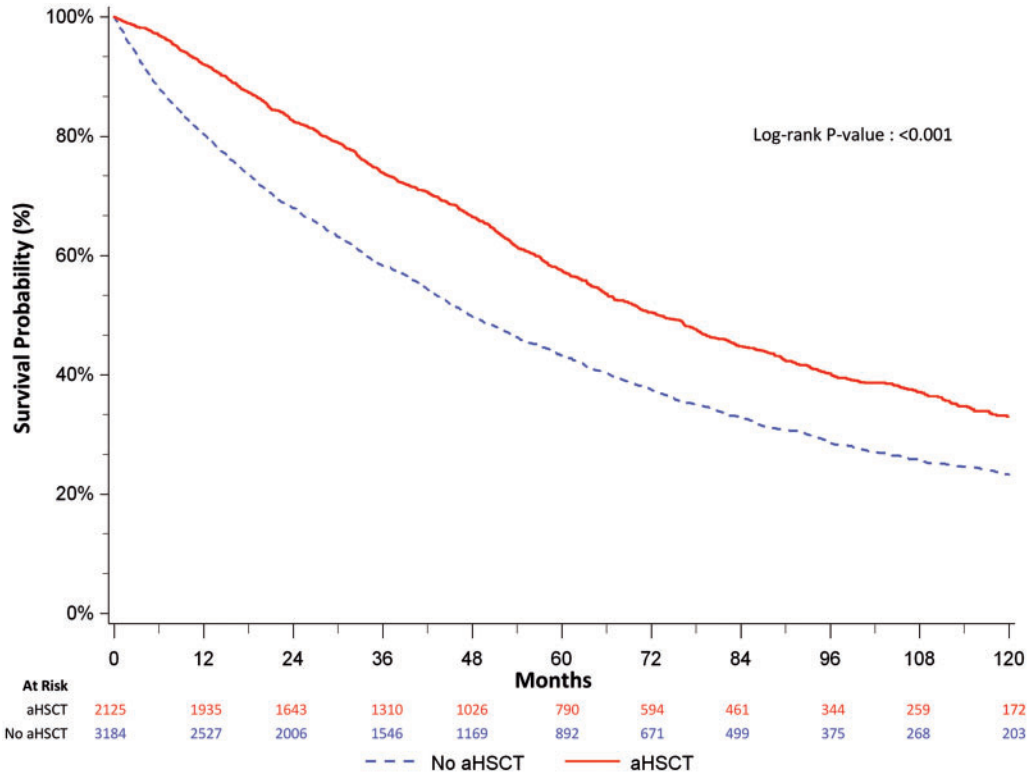

Figure 2. Overall survival from time of autologous hematopoietic stem cell transplant (aHSCT). Autologous hematopoietic stem cell transplant patients were matched to non-aHSCT patients in a ratio of up to 1:2 on age at diagnosis, sex, race/ethnicity, neighborhood socioeconomic status, and comorbidities. Survival times are estimated using the Kaplan-Meier method from the date of transplant among aHSCT patients. Each non-aHSCT patient had to be alive at the time of the matched transplant, and survival times were estimated from this point forward. Differences between the survival curves were tested using the two-sided log-rank test. aHSCT = autologous hematopoietic stem cell transplant.

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Table 2. The effect of autologous hematopoietic stem cell transplant on the hazard of death and disease-specific mortality

Modeling strategy	Adjusted HR* (95% CI)	P†
Overall survival		
Inverse probability weighting	0.83 (0.75 to 0.92)	.004
Propensity score matched	0.70 (0.65 to 0.75)	<.001
Traditional regression	0.68 (0.64 to 0.73)	<.001
Disease-specific survival		
Inverse probability weighting	0.91 (0.81 to 1.03)	.14
Propensity score matched	0.73 (0.68 to 0.80)	<.001
Traditional regression	0.72 (0.67 to 0.78)	<.001

*Adjusting for: sex, race/ethnicity, age at diagnosis, neighborhood socioeconomic status, marital status, insurance type, firstline therapy, rural vs urban location, year of diagnosis. CI = confidence interval; HR = hazard ratio.
†Adjusted hazard ratios were estimated using multivariable Cox proportional hazards regression analysis. All statistical tests were two-sided.

(aHR = 1.33, 95% CI = 1.16 to 1.51). These findings were consistent with the propensity score–matched (aHR = 1.26, 95% CI = 1.11 to 1.43) and traditional regression models (aHR = 1.25, 95% CI = 1.10 to 1.42).

Discussion

In this population-based study of more than 13 000 newly diagnosed multiple myeloma patients, aHSCT use was associated with improvements in OS that persisted across the treatment eras that included the rapid adoption of immunomodulatory agents and proteasome inhibitors. Autologous HSCT was utilized in 20.8% of patients age 18 to 79 years at diagnosis, with increases in the use of aHSCT from 15.4% to 23.9% over the study period. Only 37.6% of those diagnosed younger than age 60 years underwent aHSCT. As individuals in this age group were included in prior studies of aHSCT and were less likely to have comorbidities precluding its use, we were surprised that so few proceeded to transplant at any time during their treatment course. Importantly, the effect of aHSCT did not differ across age groups, implying that older adults benefit from aHSCT as much as younger patients. In this group, aHSCT was even less common: 11.5% of patients diagnosed at age 60 years and older underwent aHSCT at any time during their treatment. The findings from our study indicate that aHSCT remains an effective treatment modality for eligible patients in the era of efficacious induction therapies.

These results, performed in a US population, corroborate the benefits of aHSCT on OS seen in two recently published European randomized clinical trials. Both clinical trials utilized the combination of lenalidomide and dexamethasone as induction, followed by double aHSCT as consolidation, compared with consolidation with melphalan, prednisone, and lenalidomide (8) or cyclophosphamide, dexamethasone, and lenalidomide (7). OS in both studies was improved at four years in the aHSCT arms (82% [8] and 86% [7] in the two trials, respectively) compared with chemotherapy consolidation (65% [8] and 73% [7] in the two trials, respectively), corresponding to an approximately 50% reduction in the hazard for death. In comparison,

Table 3. The effect of aHSCT on overall survival across treatment eras among California multiple myeloma patients, 1998–2012

	IPW		Propensity score matched		Traditional Cox	
Era	HR* (95% CI)	P†	HR (95% CI)	P†	HR (95% CI)	P†
1998–2002	0.97 (0.84 to 1.11)	.61	0.81 (0.72 to 0.90)	<.001	0.81 (0.73 to 0.89)	<.001
2003–2007	0.72 (0.60 to 0.86)	<.001	0.68 (0.62 to 0.76)	<.001	0.66 (0.60 to 0.73)	<.001
2008–2012	0.81 (0.61 to 1.08)	.15	0.53 (0.45 to 0.62)	<.001	0.53 (0.45 to 0.62)	<.001
$P_{interaction}$‡	.29		<.001		<.001	

*Adjusting for: sex, race/ethnicity, age at diagnosis, neighborhood socioeconomic status, marital status, insurance type, firstline therapy, rural vs urban location, year of diagnosis. aHSCT = autologous hematopoietic stem cell transplant; CI = confidence interval; HR = hazard ratio; IPW = inverse probability weighting.
†Adjusted hazard ratios were estimated using multivariable Cox proportional hazards regression analysis. All statistical tests were two-sided.
‡To test whether the effect of aHSCT differed by era, multivariable Cox proportional hazards regression models were fit with an interaction between Era and aHSCT use, adjusted for baseline patient characteristics as above. All statistical tests were two-sided.

the effect seen in this study is modest. Inclusion of patients who would not have met admission criteria to the clinical trial, or to differences between the induction regimens used in this US cohort compared with those used in Europe, may explain these differences. Double aHSCT is not widely employed in the United States, while bortezomib, which is frequently used in the United States, was not utilized in either trial. Therefore, neither trial is directly generalizable to US populations. The recently reported IFM 2009 trial of up-front compared with deferred aHSCT in patients undergoing induction therapy with lenalidomide, bortezomib, and dexamethasone addresses these issues. PFS was statistically significantly longer in the aHSCT arm (36 months vs 50 months). OS did not differ between the two arms: at four years, 82% and 81% of the non-aHSCT and aHSCT patients were alive, respectively (11). Crossover rates differed greatly between these three clinical trials. In the earlier European trials, 43% (7) and 63% (8) of patients randomly assigned to the non-aHSCT arm underwent aHSCT after relapse. In the IFM 2009 trial, 79% of patients randomly assigned to the non-aHSCT arm underwent crossover. This would imply that the timing of aHSCT does not matter, as long as it remains available to patients at some point during their treatment course. The ongoing DFCI 2009 study will provide additional information about early vs late aHSCT in the US population using continuous maintenance therapy. In the current study, 65.7% of all aHSCTs were performed within one year of diagnosis, and 88.7% of all aHSCTs occurred within two years of diagnosis. Thus, real-world "crossover" is uncommon: most patients either undergo aHSCT as part of their initial therapy or not at all.

In two retrospective series comparing survival from time of diagnosis among aHSCT recipients who underwent transplant either early (defined as <12 months after diagnosis) or late (≥12 months after diagnosis), overall survival did not differ between groups (28,29). Neither study, however, accounted for immortal time bias, which would bias the results favoring a delayed transplant by guaranteeing survival at least until the late aHSCT. The current study used the same definitions of early and late transplant, but accounted for immortal time bias by including aHSCT as a time-dependent covariate. While our intent was to differentiate between aHSCT utilized as part of first- vs second-course therapy, our results should be interpreted with caution. Late aHSCT may have been due to resistant disease or early relapses, which could bias the results in favor of early aHSCT use, and demographic factors affect timing of aHSCT use (30).aHSCT utilization rates in the current study were slightly more common than in prior reports. A Center for International Blood and Marrow Transplant Research analysis estimated that 13% of newly diagnosed multiple myeloma patients underwent aHSCT, with 9% undergoing aHSCT within 12 months of diagnosis (31). A National Cancer Database Analysis reported that 9% of patients underwent aHSCT as part of first-course therapy (32). The current study was enriched for transplant-eligible patients by including only those younger than age 80 years, resulting in an overall aHSCT utilization rate of 20.8%. By using two data sources linked at the patient level, we may have been able to more accurately ascertain late aHSCT use than prior studies. Compared with prior reports, our aHSCT cohort had a similar age and sex distribution, but fewer African Americans (11.2% vs 13%–15% [31] and 14% [32]) and more Hispanics (21.2% vs 4%–5% [31] and 5% [32]) and Asians (9.3% vs 2% [32]). Younger patients and those with fewer comorbidities were more likely to undergo HSCT, as were those with private compared with governmental or no insurance (30).

The current study has several limitations. The CCR does not collect data on multiple myeloma stage, cytogenetics, molecular information, specific treatment regimens (including agents and dosing) or disease response, all of which likely contribute to the decision to proceed, or not to proceed, to transplant. This may be of particular relevance to analyses comparing earlier with later aHSCT. Chemotherapy use is likely to be under-reported in the cancer registry (33,34), but it is unlikely that this under-reporting differs between aHSCT and non-aHSCT recipients; it may be related to other unrecorded patient characteristics (eg, performance status) in our study. Indeed, in sensitivity analyses excluding patients without chemotherapy, our associations of aHSCT and survival were even stronger (data not shown). In addition, as the CCR only captures initial treatment modalities, we cannot determine specific transplant-preparative regimens, which are likely to be melphalan based, but could also include experimental regimens or additional chemotherapy agents or radiation therapy. Disease-specific survival is based on death certificate data and is thus prone to misclassification.

Nonetheless, this study offers several strengths. Patients included in clinical trials may not represent those typically seen in routine clinical practice (12,13,35). For example, clinical trials of aHSCT have excluded patients older than age 65 years, provided no information on race/ethnicity, or excluded patients with multiple comorbidities (7,8,11,36). Observational research studies provide complementary data on the generalizability of findings from clinical trials. In a population-based study using SEER-Medicare data, aHSCT use among multiple myeloma patients older than age 65 years was associated with improved OS and was found to be cost-effective (18,19). The current study corroborates these findings, with no differences found in the

effect of aHSCT in different age groups, including those older than age 65 years. Furthermore, we utilized propensity-based analytic methods to mitigate the inherent confounding by indication in retrospective studies of a treatment effect, and we relied on the conservative analytic approach, IPW-adjusted models, to base our conclusions (37).

In conclusion, this population-based study corroborates results of prior randomized controlled and observational studies: aHSCT is associated with improved OS. Overall, aHSCT is utilized infrequently, warranting future studies focusing on access and barriers to aHSCT. In an era of new efficacious and less intense therapeutic approaches, aHSCT should remain a standard approach in the treatment of eligible, newly diagnosed multiple myeloma patients.

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Notes

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Author contributions: design and conception: ASR, AB, BAJ, TK, TW; acquisition of data and analysis: AB; drafting of the manuscript: ASR, TW; final review and approval: ASR, AB, BAJ, TK, TW.

Conflicts of interest: ASR is on the speakers bureau for Amgen.

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