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Chemotherapy and Survival for Patients With Multiple Myeloma

Findings From a Large Nationwide and Population-Based Cohort

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Objective: To assess the patterns of chemotherapy use for patients with multiple myeloma and to determine if chemotherapy is effective in prolonging survival outside the clinical trial settings.

Methods: We studied a nationwide and population-based retrospective cohort of 4902 patients ≥65 years of age with stage II or III multiple myeloma from 1992 to 1999, identified from the Surveillance, Epidemiology, and End-Results-Medicare data. Multivariate logistic regression was used to estimate the odds ratio of receiving chemotherapy and Cox proportional hazard model was used to estimate the hazard ratio of mortality associated with chemotherapy.

Results: Of 4902 patients with stage II or III multiple myeloma, 52.0% received chemotherapy during the course of the disease. The receipt of chemotherapy decreased significantly with age from 65.7% in the 65- to 69-year age group to 34.3% in those ≥80 years. Blacks (47.6%) were less likely to receive chemotherapy than whites (52.8%). Use of chemotherapy decreased significantly with comorbidity scores and increased over time. Risk of all-cause mortality was significantly reduced in patients who received chemotherapy compared with those who did not (adjusted hazard ratio = 0.65; 95% confidence interval = 0.61–0.69). A similar pattern as observed for myeloma-specific mortality (0.61; 0.56–0.67). Survival benefit increased with increasing cycles of chemotherapy ($P < 0.001$ for trend) and was significant across different age groups, gender, ethnic groups, and comorbidity scores.

Conclusion: Chemotherapy was significantly associated with increased survival in patients with multiple myeloma outside the clinical trial settings. This survival benefit was significant across different groups by age, gender, race, and comorbidity. A substantial number of patients with multiple myeloma did not receive chemotherapy.

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Multiple myeloma, a cancer of the plasma cell, is the second most prevalent hematologic cancer in the United States, after non-Hodgkin's lymphoma.[1,2] The American Cancer Society estimated that there will be 16,570 new cases of multiple myeloma in the United States in 2006 and about 11,310 patients are estimated to die of multiple myeloma, accounting for 2% of all cancer deaths.[1,2] This disease primarily affects the elderly population as the median age of incidence was 70 years and the median age of death was 74 years.[1,2] While the incidence is higher in blacks than whites and other ethnic populations,[1–3] the etiology of this disease is largely unknown.[4–16]

Standard therapy for elderly patients with multiple myeloma has been melphalan plus prednisone (MP) for several decades.[17–23] For patients younger than 65 years, high-dose chemotherapy and induction therapy followed by autologous stem-cell transplantation is recommended as the first line therapy.[24–29] More recent studies found that combination chemotherapy regimens with melphalan may prove superior.[30–33] Although chemotherapy has been well documented to be efficacious in prolonging survival in clinical trials, little is known about how chemotherapy is practiced among patients living in the community and whether this therapy is also effective outside the clinical trial settings. Elderly patients have been disproportionately under-represented in the clinical trials, yet this population accounts for most cancer cases.[34–37] Therefore, we undertook a large nationwide and population-based study in elderly patients diagnosed with multiple myeloma in 11 areas of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) tumor registries to determine what proportion of patients received chemotherapy as recommended, what factors were associated with not receiving this therapy, and whether chemotherapy was effective in prolonging survival among elderly patients outside the clinical trial settings.

PATIENTS AND METHODS

Data Sources

We used the SEER-Medicare linked data for cases diagnosed with multiple myeloma in 1992–1999. The SEER program, supported by the National Cancer Institute, includes population-based tumor registries in 11 selected geographic areas[1,38,39]: the metropolitan areas of San Francisco/Oakland, Detroit, Atlanta and Seattle; Los Angeles county; the San Jose-Monterey area; and the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, covering over 14% of the U.S. population. The registries ascertain all newly diagnosed multiple myeloma cases from multiple reporting sources, such as hospitals, outpatient clinics, laboratories, private medical practitioners, nursing/convalescent homes/hospices, autopsy reports, and death certificates.

The Medicare program provides payments for hospital, physician, and outpatient medical services for more than 97% of persons 65 years of age or older.[38,39] Medicare claims data are available through 2002. For persons aged 65 years or older appearing in the SEER records, Medicare eligibility could be identified for 94% of these cases. The method of linking these data has been described elsewhere.[38,39] The Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved this study.

Study Population

Our study was based on the analytical SEER-Medicare files that excluded patients who did not have full coverage of both Medicare Part A and Part B to ensure the completeness of their Medicare claims, and those who were members of health maintenance organizations because Medicare claims of these patients may be incomplete. We studied 4902 patients with late stage (Durie-Salmon stage II or III) multiple myeloma because these patients represented over 90% of all cases with multiple myeloma and chemotherapy was universally recommended for these patients.[17–27] In this database, there were also 146 patients with early-stage (Durie-Salmon stage I) multiple myeloma who were generally asymptomatic and were often recommended for a period of active observation instead of chemotherapy,[26] whose treatment recommendations are not homogeneous. Therefore, these small numbers of cases were excluded from further analyses.

Outcome Variables

Survival time in months was calculated from the date of diagnosis to the date of death or to the date of last follow-up (December 31, 2002). The cause of death is identified by the SEER program through linking the SEER data with the National Death Index data from the National Center for Vital Statistics. All-cause mortality was defined as death from any cause indicated in the SEER registry data. Patients still alive at the last date of follow-up were censored in the time to event survival analysis by the Kaplan-Meier method and Cox proportional hazard regression model. Multiple myeloma-specific mortality was defined as multiple myeloma as the underlying cause of death. In this cause-specific analysis, patients who died of causes other than multiple myeloma or who were still alive at the date of last follow-up were censored.

Treatment of Multiple Myeloma

Chemotherapy

Detailed methods for the identification of chemotherapy use through Medicare claims have been previously described.[40,41] In brief, patients with cancer were defined as having received chemotherapy if any of the following Medicare procedure codes so indicated during the course of the disease: the ICD-9-CM procedure code of 99.25 and V codes of V58.1, V66.2, or V67.2; the common procedure codes of 96400-96549, J8530-J8999, or J9000-J9999, or Q0083-Q0085, and revenue center codes of 0331, 0332 and 0335.[42–45] The commonly used chemotherapy drug includes melphalan (J9245 or J8600). Since melphalan (plus prednisone) is standard therapy and several combination chemotherapy regimens yielded similar survival benefit, we included these patients as having received chemotherapy and did not specify specific drug therapy.

Radiation Therapy

Patients were defined as having received radiation therapy if either SEER or Medicare claims so indicated.[46]

Stem Cell Transplantation

Patients were defined as having received stem cell transplantation if the following Medicare claims indicated so: ICD-9-CM codes of 4100–4109, or CPT codes of 38230, 38231, 38240, and 38241.[42–45] Because only 41 (0.8%) cases received it and it was not recommended in the elderly patients, this variable was not included in the final analysis.

Socioeconomic Status

The percent of persons living below the poverty line at the census tract level from the 1990 census available in the SEER-Medicare linked data was used to define socioeconomic status. This variable was selected because for elderly Medicare beneficiaries, the poverty level could be the most directly relevant proxy measure of their economic status.[47] Two other socioeconomic variables (percent of adults aged ≥25 who had less than 12 years of education and median annual household income at the census tract level) were also examined in the analysis in place of poverty. Because these 2 socioeconomic measures yielded the similar results, only the results using poverty were reported.

Comorbidity Score

Comorbidity was ascertained from Medicare claims by identifying 18 comorbid diagnoses between one year prior to and one month after the diagnosis of multiple myeloma. Details on creating a weighted comorbidity score have been previously reported.[48]

Other Characteristics

Patient and tumor characteristics such as age at diagnosis (categorized as 65–69, 70–74, 75–79, ≥80 years), gender, race/ethnicity (white, black, and others), year of diagnosis (1992–1999), and geographic area (11 SEER areas) available from SEER were assessed as correlates of the receipt of chemotherapy and survival.

Statistical Analysis

Differences in the distribution of baseline characteristics between patients who received chemotherapy and those who did not were tested using the χ^2 statistic, odds ratios (ORs), and associated 95% confidence intervals (CIs). The 3-year observed survival rate was the proportion of patients who survived for at least 3 years in those diagnosed in 1992 to 1999, and the 5-year observed survival rate was the proportion of patients who survived for at least 5 years in those diagnosed in 1992 to 1997. Patients who were lost to follow-up, withdrawn, or still alive at the last date of follow-up (December 31, 2002) were censored in the time to event survival analysis using the Kaplan-Meier method and Cox proportional hazard model.[49–51] In multiple myeloma-specific mortality analysis, patients who died of causes other than multiple myeloma were additionally censored. The median survival time with 95% confidence interval was estimated from the Kaplan-Meier survival curve using the LIFETEST procedure.[49,50]

Cox proportional hazard regression model was used for survival analysis using the PHREG procedure available in the SAS system.[50] The proportionality assumption was considered to be satisfied when the log-log Kaplan-Meier curves for survival functions by the receipt of chemotherapy were parallel and did not intersect.[51] Multiple Cox regression analyses were adjusted for age, gender, race/ethnicity, radiation therapy, comorbidity score, year of diagnosis, geographic area, and socioeconomic status.

RESULTS

Table 1 presents the distribution of the 4902 elderly patients with stage II or III multiple myeloma and the comparison between those who received chemotherapy and those who did not, by age, gender, race/ethnicity, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and geographic area. Median age at diagnosis in these patients was 76 years, ranging from 65 to 104 years. Median age was 78 years for those who did not receive chemotherapy compared with 74 years for those who received chemotherapy. The distribution of patients who received chemotherapy was different from those who did not in terms of age, comorbidity, radiation therapy, year of diagnosis and geographic area, but there was no significant difference in terms of gender, race/ethnicity, and socioeconomic status.

Table 2 presents the number and percentage of patients receiving chemotherapy for all patients and stratified by other factors, and also presents the adjusted odds ratios of receiving chemotherapy. Overall, 52.0% of patients with stage II or III multiple myeloma received chemotherapy during the course of the disease. The receipt of chemotherapy decreased substantially by age from 65.7% in patients 65 to 69 years of age to 34.3% in those ≥80 years of age. After adjusting for gender, ethnicity, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and geographic areas, patients 70 to 79 years of age were 41% less likely to receive chemotherapy (OR = 0.59; 95% CI, 0.49–0.70) compared with patients 65 to 69 years of age. There was no significant difference in the use of chemotherapy between men and women. Black patients were 23% less likely to receive chemotherapy compared with whites. The receipt of chemotherapy decreased significantly with increased comorbidity scores, and those with comorbidity scores of 3 or higher were almost twice as likely to receive no chemotherapy. Patients who received radiation therapy were also more likely to receive chemotherapy. The rate of receiving chemotherapy decreased slightly from high to low socioeconomic status, and increased significantly over time from 1992 to 1999. There were also some geographic variations in the 11 SEER registries.

Among 4902 patients included in this cohort who were followed up for at least 3 years and up to 11 years (median follow-up, 7.1 years), the 3-year overall observed survival rate was 56.0% (2747 of 4902), and the 3-year multiple myeloma-specific observed survival rate was 73.7% (3614 of 4902). The 5-year overall and myeloma-specific observed survival rates were 43.6% (1664 of 3814) and 60.8% (2318 of 3184), respectively, among those patients who were diagnosed in 1992 to 1997 and followed up for at least 5 years. Based on the Kaplan-Meier survival curve, the median survival time was 5.9 years (95% CI, 5.6–6.2) for patients receiving chemotherapy and 1.6 years (95% CI, 1.4–1.8) for those who did not receive chemotherapy.

Table 3 presents the number and percent of observed death within 3 years of diagnosis and by the date of last follow-up, and also presents the adjusted hazard ratio of mortality in association with the receipt of chemotherapy as well as the number of cycles of chemotherapy (measured by the number of claims for chemotherapy). The crude death rates within 3 years of diagnosis and by the last follow-up were lower in those who received chemotherapy than those who did not. After adjusting for other potential confounding factors, patients who received chemotherapy were 35% less likely to die of all-causes (hazard ratio = 0.65; 95% CI, 0.61–0.69) and 41% less likely to die of multiple myeloma (hazard ratio = 0.61; 95% CI, 0.56–0.67) than those who did not receive chemotherapy. The risk of call-cause mortality and myeloma-specific mortality decreased with increasing number of chemotherapy cycles ($P < 0.001$ for trend). For example, compared with patients who did not receive chemotherapy, those who received 1 to 5 cycles were 16% less likely to die of all-causes, whereas those who received 25 to 35 cycles were 53% less likely to die, after adjusting for age, gender, race, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and geographic area.

Figure 1 presents the Cox proportional hazard ratios (95% CI) of all-cause and multiple myeloma-specific mortal-

TABLE 1. Comparison of Characteristics Between Patients With Multiple Myeloma Who Received Chemotherapy and Those Who Did Not (1992–1999)

Characteristic	No. of Patients	% of Patients	Column % of Patients, Stratified by the Receipt of Chemotherapy		*P* for Difference Between 2 Groups
			Did Not Receive Chemotherapy	Received Chemotherapy	
Age (yr) [median (range)]	76 (65–104)		78 (65–104)	74 (65–95)	
Age (yr)					
65–69	1018	20.8	14.8	26.3	<0.001
70–74	1161	23.7	18.2	28.7	
75–79	1179	24.1	23.9	24.2	
≥80	1544	31.5	43.1	20.8	
Gender					
Male	2355	48.0	46.8	49.2	0.082
Female	2547	52.0	53.2	50.8	
Race/ethnicity					
White	3893	79.4	78.1	80.6	0.100
Black	676	13.8	15.0	12.6	
Others	333	6.8	6.9	6.7	
Comorbidity scores					
0	2292	46.8	40.9	52.1	<0.001
1	1117	22.8	24.0	21.6	
2	707	14.4	15.1	13.8	
≥3	786	16.0	19.9	12.5	
Radiation therapy					
No	3579	73.0	78.9	67.6	<0.001
Yes	1323	27.0	21.2	32.4	
Socioeconomic status (SES)					
1st quartile (high SES)	1211	24.7	23.4	25.9	0.103
2nd quartile	1213	24.8	23.9	25.5	
3rd quartile	1256	25.6	26.7	24.6	
4th quartile (low SES)	1132	23.1	24.4	21.9	
Missing	90	1.8	1.6	2.0	
Year of diagnosis					
1992	689	14.1	16.0	12.3	<0.001
1993	609	12.4	13.3	11.7	
1994	632	12.9	13.8	12.1	
1995	598	12.2	11.4	12.9	
1996	656	13.4	12.9	13.9	
1997	630	12.9	12.4	13.3	
1998	547	11.2	10.2	12.0	
1999	541	11.0	10.1	11.9	
SEER registry areas					
San Francisco, CA	380	7.8	8.1	7.4	<0.001
Connecticut	653	13.3	15.3	11.5	
Detroit, MI	907	18.5	18.7	18.3	
Hawaii	91	1.9	2.0	1.7	
Iowa	704	14.4	14.8	14.0	
New Mexico	214	4.4	4.2	4.6	
Seattle, WA	531	10.8	9.7	11.9	
Utah	260	5.3	5.4	5.2	
Atlanta, GA	277	5.7	4.9	6.3	
San Jose-Monterey, CA	210	4.3	4.3	4.2	
Los Angeles, CA	675	13.8	12.6	14.8	
Total	4902	100.0	100.0	100.0	

TABLE 2. Percentage and Odds Ratio of Receiving Chemotherapy in Patients With Multiple Myeloma

Characteristic	No. of Patients	No. of Patients Receiving Chemotherapy	% of Patients Receiving Chemotherapy	Adjusted Odds Ratio* (95% Confidence Interval) of Receiving Chemotherapy
All patients	4902	2547	52.0	
Age (yr)				
65–69	1018	669	65.7	1.00
70–74	1161	732	63.1	0.91 (0.76–1.09)
75–79	1179	617	52.3	0.59 (0.49–0.70)
≥80	1544	529	34.3	0.29 (0.24–0.34)
Gender				
Male	2355	1254	53.3	1.00
Female	2547	1293	50.8	0.99 (0.88–1.12)
Race/ethnicity				
White	3893	2054	52.8	1.00
Black	676	322	47.6	0.77 (0.63–0.95)
Others	333	171	51.4	0.86 (0.67–1.12)
Comorbidity scores				
0	2292	1328	57.9	1.00
1	1117	551	49.3	0.80 (0.68–0.93)
2	707	351	49.7	0.81 (0.68–0.97)
≥3	786	317	40.3	0.54 (0.45–0.64)
Radiation therapy				
No	3579	1722	48.1	1.00
Yes	1323	825	62.4	1.53 (1.34–1.76)
Socioeconomic status (SES)				
1st quartile (high SES)	1211	660	54.5	1.00
2nd quartile	1213	650	53.6	0.91 (0.77–1.09)
3rd quartile	1256	627	49.9	0.77 (0.64–0.92)
4th quartile (low SES)	1132	558	49.3	0.84 (0.69–1.02)
Missing	90	52	57.8	1.15 (0.72–1.84)
Year of diagnosis				
1992	689	313	45.4	1.00
1993	609	297	48.8	1.09 (0.86–1.37)
1994	632	307	48.6	1.13 (0.90–1.42)
1995	598	329	55.0	1.57 (1.24–1.98)
1996	656	353	53.8	1.52 (1.21–1.90)
1997	630	339	53.8	1.65 (1.31–2.08)
1998	547	306	55.9	1.66 (1.31–2.11)
1999	541	303	56.0	1.68 (1.32–2.13)
SEER registry areas				
San Francisco, CA	380	189	49.7	1.00
Connecticut	653	293	44.9	0.65 (0.49–0.85)
Detroit, MI	907	467	51.5	0.97 (0.75–1.26)
Hawaii	91	44	48.4	0.80 (0.48–1.32)
Iowa	704	356	50.6	0.96 (0.73–1.26)
New Mexico	214	116	54.2	0.95 (0.66–1.37)
Seattle, WA	531	303	57.1	1.12 (0.84–1.48)
Utah	260	132	50.8	0.87 (0.62–1.21)
Atlanta, GA	277	161	58.1	1.29 (0.92–1.80)
San Jose–Monterey, CA	210	108	51.4	0.86 (0.60–1.23)
Los Angeles, CA	675	378	56.0	1.28 (0.98–1.67)

*Adjusted for variables listed in the table.

TABLE 3. Effect of Chemotherapy and the Number of Cycles of Chemotherapy on Mortality in Patients With Multiple Myeloma With up to 11 Years of Follow-up

Chemotherapy Status	No. of Patients (n = 4902)	No. (%) of Observed Deaths Within 3 Years	No. (%) of Observed Death by Last Follow-up	Hazard Ratio* (95% CI) of Mortality	*P*
All-cause mortality					
All patients					
No chemotherapy	2355	1458 (61.9)	2189 (93.0)	1.00 (reference)	—
Receipt of chemotherapy	2547	697 (27.4)	2313 (90.8)	0.65 (0.61–0.69)	<0.001
Cycle (no. of claims) of chemotherapy received					
0 (no chemotherapy)	2355	1458 (61.9)	2189 (93.0)	1.00 (reference)	—
1–5	1067	498 (46.7)	1010 (94.7)	0.84 (0.77–0.90)	<0.001
6–15	643	136 (21.2)	571 (88.8)	0.63 (0.57–0.69)	<0.001
16–25	298	32 (10.7)	264 (88.6)	0.55 (0.48–0.62)	<0.001
25–35	172	14 (8.1)	147 (85.5)	0.47 (0.40–0.56)	<0.001
>35	367	17 (4.6)	321 (87.5)	0.45 (0.40–0.51)	<0.001
Myeloma-specific mortality					
All patients					
No chemotherapy	2355	861 (36.6)	1101 (46.8)	1.00 (reference)	—
Receipt of chemotherapy	2547	427 (16.8)	1019 (40.0)	0.61 (0.56–0.67)	<0.001
Cycle (no. of claims) of chemotherapy received					
0 (no chemotherapy)	2355	861 (36.6)	1101 (46.8)	1.00 (reference)	—
1–5	1067	310 (29.1)	501 (47.0)	0.83 (0.75–0.93)	<0.001
6–15	643	84 (13.1)	248 (38.6)	0.58 (0.51–0.67)	<0.001
16–25	298	16 (5.4)	98 (32.9)	0.44 (0.36–0.54)	<0.001
25–35	172	7 (4.1)	51 (29.7)	0.38 (0.28–0.50)	<0.001
>35	367	10 (2.7)	121 (33.0)	0.34 (0.28–0.41)	<0.001

*Hazard ratio (95% confidence internal) was the time to event analysis by censoring those who were lost to the follow-up or still alive at the end of follow-up, and simultaneously adjusting for age, gender, race, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and SEER areas.

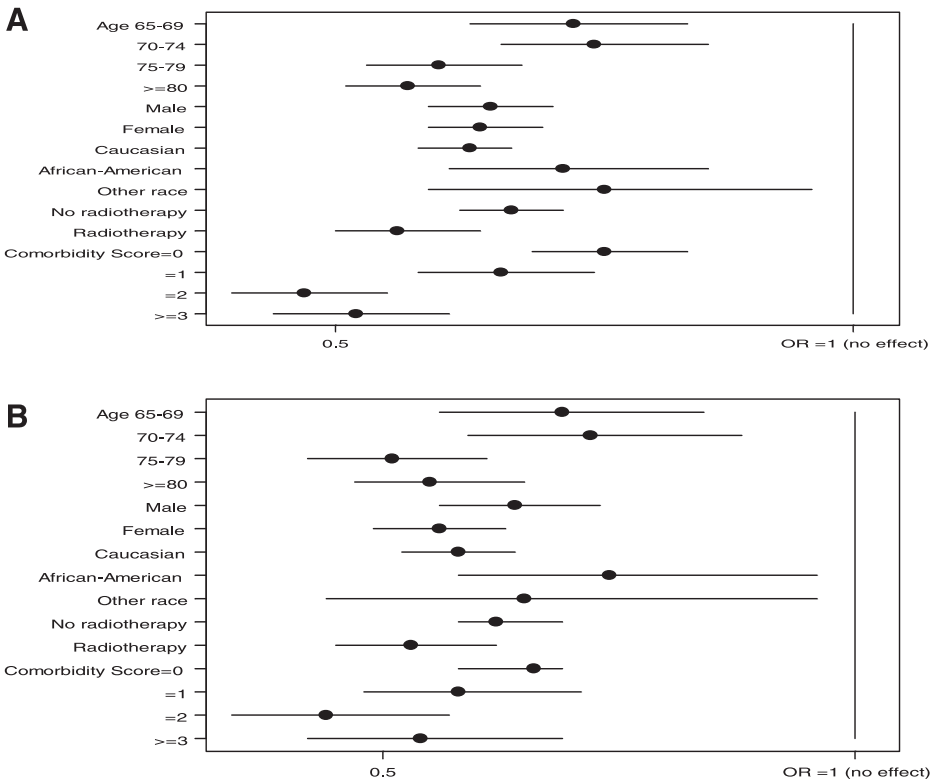

FIGURE 1. Hazard ratio (95% confidence interval) of all-cause (A) and myeloma-specific (B) mortality in patients with stage II to III multiple myeloma who received chemotherapy compared with those who did not, stratified by age, gender, race, radiotherapy, and comorbidity score.

ity in patients who received chemotherapy compared with those who did not, stratified by selected demographic factors and radiation therapy. This was to determine whether the pattern of improved survival associated with chemotherapy was held within strata of these factors. Survival benefit of chemotherapy was statistically significant in all strata of age, gender, race, comorbidity, and radiation therapy. For example, the hazard ratio of all-cause mortality was 0.63 (95% CI, 0.58–0.67) in white patients with chemotherapy compared with those without, whereas corresponding hazard ratio was 0.72 (95% CI, 0.61–0.86) for blacks. Similarly, chemotherapy was associated with 25% to 40% reduction in mortality, regardless of comorbidity scores.

DISCUSSION

It is important to assess whether the clinical treatment guidelines for the receipt of chemotherapy as the standard of care for elderly patients with stage II or III multiple myeloma were being followed in the community practices and whether any lack of appropriate therapy was associated with decreased survival. We found that receiving chemotherapy was associated with 35% survival advantage, and this survival benefit was significant across different age groups, ethnic groups, gender, and comorbidity scores. However, a large proportion of the elderly patients with stage II or III multiple myeloma did not receive chemotherapy and the receipt of chemotherapy decreased substantially with age.

Age is a major factor in determining cancer therapies.[52–57] Several studies demonstrated that older patients with breast cancer and colon cancer were significantly less likely to receive chemotherapy according to the clinical guidelines.[52,56,57] Nonreceipt of chemotherapy among elderly patients has been attributed to the lack of healthcare access.[58] However, in our study, all patients had access to Medicare so that these patients can be entitled for inpatient and outpatient medical services across the United States. There were some inconsistent findings about whether elderly patients were as likely to tolerate the chemotherapy-related toxicities as younger patients.[59–62] Currently, many patients who receive chemotherapy often receive antiemetics,[63] and more patients receive hematopoietic growth factors to prevent more serious toxicities such as neutropenia and anemia.[62,63] Nevertheless, our study was consistent with previous reports, showing that older patients were less likely to receive chemotherapy. Since chemotherapy was associated with increased survival rate in all age groups of the elderly patients with multiple myeloma, it is therefore concerning if age is still a barrier to the recommended therapy.

The Institute of Medicine has demonstrated convincing and substantial disparities in the quality of health care among various race/ethnic groups in the United States.[58] Low socioeconomic status and poor access to medical care are the main contributors in not receiving the recommended therapies. In our study, black patients (47.6%) were significantly less likely to receive chemotherapy than whites (52.8%), even after adjusting for patient demographics and radiation therapy. Although a larger proportion of blacks lived in the lowest quartile of socioeconomic status, ethnic difference in the receipt of chemotherapy did not change after adjusting for socioeconomic status. Healthcare providers may also be a factor in the disparities of receiving the standard of care.[64] However, outcomes in patients with multiple myeloma were similar across the ethnic groups as found in this as well as in other studies.[65,66] This may be due to the fact that socioeconomic status was not significantly associated with survival in this study and ethnic difference in receiving chemotherapy was relatively small.

As we found in this study, chemotherapy was effective in prolonging survival among the community dwelling elderly patients. Although numerous clinical trials have well documented the efficacy of chemotherapy, no study has been conducted to evaluate the effectiveness of chemotherapy in elderly patients outside the clinical trial settings. To the best of our knowledge, this study is the first to demonstrate that the efficacy of chemotherapy documented in clinical trials settings has been translated into the "real world" effectiveness. This has a number of clinical and public health implications. First, patients enrolled in the clinical trials were often motivated volunteers and highly selected because only those relatively healthy patients with minimal comorbidity can be eligible for the trials. Therefore, these patients are often not representative of all the patients outside the clinical settings. Our study documented that chemotherapy is also beneficial for patients in the community. Second, elderly patients, particularly oldest old (≥80 years), are often underrepresented in the clinical trials.[34–37] It is often uncertain if the efficacy documented in younger patients can still be generalizable to older ones. Findings from a large cohort of elderly patients in this study suggested that survival benefit was evident even in those very old patients as well. Furthermore, in tumors such as breast cancer, survival benefit decreased with advanced age due to decreased tumor sensitivity, inadequate dosage for the elderly patients, or concern about lack of abilities in tolerating toxicity. However, our study showed that oldest old patients can still benefit significantly from chemotherapy. Survival benefit was significant in those without comorbid conditions as well as in those with comorbid diseases.

Several limitations need to be noted. First, the study population only included patients 65 years of age or older who are not health maintenance organization members and who have both Medicare Part A and Part B coverage. Findings may not be generalizable to a younger population. However, because multiple myeloma is essentially a disease of the elderly, the study findings may be applied to a large number of cases. Targeting this population would have great importance for much-needed research in identifying health problems and for improving quality of life. Second, we are unable to determine the actual doses of chemotherapy given. However, we provided an estimate on the number of cycles for receiving chemotherapy that was associated with decreasing mortality. Those who received more cycles of chemotherapy appeared to have greater benefits in mortality reduction. Furthermore, information on the receipt of chemotherapy was

based on Medicare claims for diagnostic and procedure codes. There might be a possibility of missing claims for chemotherapy in Medicare data, although overcoding on chemotherapy may be unlikely.[41] Finally, socioeconomic status was based on the 1990 census tract level. Although poverty, education, and household income at the census tract level provided similar findings, there may be residual confounding when the individual level socioeconomic status was not adjusted for in the analysis.

CONCLUSION

Chemotherapy was significantly associated with increased survival in patients with multiple myeloma outside the clinical trial settings. This survival benefit was significant across different ages, gender, and comorbidity. However, substantial number of patients with stage II or III multiple myeloma (48%) did not receive chemotherapy. Additional studies to confirm these findings in younger populations and to incorporate the quality of life issues may be helpful.

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