Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials

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Abstract
Multiple myeloma (MM) is an incurable hematologic malignancy with disparities in outcomes noted among racial-ethnic subgroups, likely due to disparities in access to effective treatment modalities. Clinical trials can provide access to evidence-based medicine but representation of minorities on therapeutic clinical trials has been dismal. We evaluated the impact of patient race-ethnicity in pooled data from nine large national cooperative group clinical trials in newly diagnosed MM. Among 2896 patients enrolled over more than two decades, only 18% were non-White and enrollment of minorities actually decreased in most recent years (2002–2011). African-Americans were younger and had more frequent poor-risk markers, including anemia and increased lactate dehydrogenase. Hispanics had the smallest proportion of patients on trials utilizing novel therapeutic agents. While adverse demographic (increased age) and clinical (performance status, stage, anemia, kidney dysfunction) factors were associated with inferior survival, patient race-ethnicity did not have an effect on objective response rates, progression-free, or overall survival. While there are significant disparities in MM incidence and outcomes among patients of different racial-ethnic groups, this disparity seems to be mitigated by access to appropriate therapeutic options, for example, as offered by clinical trials. Improved minority accrual in therapeutic clinical trials needs to be a priority.

Introduction
Multiple myeloma (MM) is the second most common hematologic malignancy with approximately 30,000 new patients diagnosed in the United States (U.S.) every year1. MM incidence is noted to have increased over time with a progressively younger median age at diagnosis2. At the same time, owing to a rapidly improving therapeutic landscape, death rates have been falling over the past decade with a reported 5-year survival rate of 48.5%1–4.

While these trends hold true for the U.S. population as a whole, with changing population demographics there is an increasing focus on how various population subgroups may be benefiting from survival improvement in MM. This is especially true for population subgroups by race and ethnicity, as several studies have shown that significant racial disparities exist in MM incidence and outcomes1,3–5,7. These disparities have been explored previously and a differential access to treatment as well as health-care utilization have been identified as a potential cause5,8–10. Such a finding has been especially true regarding access to stem cell transplant (SCT), a standard of care for MM treatment, which is known to be utilized much more commonly in Whites as compared to racial-
ethnic minorities\textsuperscript{5,10–12}. Nevertheless, some retrospective, single-institution and single clinical trial analyses have shown that, in equal access situations, racial disparities in outcomes may be mitigated, especially for those who receive SCT\textsuperscript{12–14}. Such an analysis has not been done on a larger, national scale across multiple clinical trials and especially not in prospectively collected data for novel therapeutic agents irrespective of SCT. We analyzed patient-level data from published Eastern Cooperative Oncology Group (ECOG)-ACRIN/South West Oncology Group (SWOG) clinical trials in newly diagnosed MM (NDMM) patients to explore the interplay of race/ethnicity and outcomes.

**Methods**

Data from nine previously published ECOG-ACRIN/SWOG clinical trials in NDMM between 1988 and 2011 was pooled for this analysis. The identified clinical trials included E1A06, E4A03, E1A00, E2A02, E5A93, E9486, S0204, S0232, and S9321. Pertinent details of the selected clinical trials are shown in Table 1. Data collected on the patients enrolled in these trials included baseline demographics (age, gender, race-ethnicity), clinical features (ECOG performance status, presence of lytic lesions, serum calcium, hemoglobin (Hb), creatinine, beta-2-microglobulin, lactate dehydrogenase (LDH), body mass index (BMI)), and MM characteristics (International Staging System (ISS) disease stage, heavy and light chain category, bone marrow plasma cell percentage). Clinical trials were grouped into fixed duration vs. treatment given to progression (including maintenance or not), with or without SCT, including a novel agent (proteasome inhibitor or immunomodulatory drug) or not, and the years of patient enrollment (1988–1991, 1992–2001, 2002–2011).

Patient were divided into mutually exclusive race-ethnicity categories, including non-Hispanic Whites (NHW), non-Hispanic African-Americans (NHAA), non-Hispanic Others (NHO), and Hispanics. Associations between race-ethnicity and categorical baseline patient, disease, and study design characteristics were assessed using the chi-square test while that between race-ethnicity and continuous baseline patient and disease characteristics were assessed using Wilcoxon test. Survival distributions since the time of enrollment were estimated based on the Kaplan–Meier method. Cox proportional hazards regression was used to estimate hazard ratios (HRs) in univariate and multivariable models. For multivariable models, covariate distribution was reviewed visually for proportional hazards. All patients were included so “missing” was included as a category, if appropriate. Wald test \( p \) values were provided from Cox regression models. Time to event data was censored at 6 years to have more uniform follow-up among the included studies. No adjustments were made for multiple testing. SAS 9.4 software was used for statistical analysis.

**Results**

A total of 3026 patients were included in the analysis from the nine selected clinical trials. Of these, 3002 patients had data available on race. Furthermore, 106 patients had missing information on ethnicity, leading to the final study cohort of 2896 patients. Patient and clinical

| Study | Phase | Intervention | N evaluable patients | % Total | Median follow-up (years)a | N survival eventsb |
|-------|-------|--------------|----------------------|--------|--------------------------|------------------|
| S9321 | 3     | VBMCP vs. Mel+TBI+SCT | 788 | 27.2 | 9.0 | 481 |
| S0204 | 2     | Thal→ Tandem SCT→ Thalidomide maintenance | 130 | 4.5 | 9.9 | 53 |
| S0232 | 3     | Dex+/-Len | 176 | 6.1 | 6.7 | 89 |
| E9486 | 3     | VBMCP vs. VBMCP+IFN α vs. VBMCP +Cyclophosphamide | 648 | 22.4 | 12.8 | 492 |
| E5A93 | 3     | VBMCP vs. VBMCP+IFN α or Cyclophosphamide | 222 | 7.7 | 9.9 | 164 |
| E1A00 | 3     | Dex+/-Thal | 205 | 7.1 | 8.0 | 128 |
| E2A02 | 2     | Bortezomib | 40 | 1.4 | 6.0 | 25 |
| E4A03 | 3     | Len+low vs. high dose Dex | 402 | 13.9 | 7.0 | 191 |
| E1A06 | 3     | Mel, Prednisone+Thal vs. Len | 285 | 9.8 | 4.9 | 159 |

VBMCP Vincristine/BCNU/Melphalan/Cyclophosphamide/Prednisone, Mel myeloablative melphalan, TBI total body irradiation, SCT stem cell transplant, Len lenalidomide, Thal thalidomide, Dex dexamethasone, IFN interferon

\textsuperscript{a}In the absence of censoring

\textsuperscript{b}Follow-up was censored at 6 years for all studies
trial characteristics are shown in Table 2. Gender distribution comprised 1693 (58.5%) males and 1203 (41.5%) females. Racial-ethnic subgroups included 2373 (81.9%) NHW, 392 (13.5%) NHAA, 76 (2.6%) Hispanics, and 55 (1.9%) NHO. Median age for the whole cohort was 61.4 years (range: 23.2–91.9 years). ISS stage was missing in 469 patients. Of the rest, ISS stage was I–II in 71.4% patients and stage III in 28.6% patients. Lytic bony lesions were present in 63.9% patients. Looking at common laboratory parameters, majority of the patients (96.2%) did not have hypercalcemia (serum calcium >12 mg/dL) and 86.8% did not have any significant elevation in serum creatinine (creatinine ≥2 mg/dL). Significant anemia (Hb ≤10 g/dL) was noted in 39.4% patients. We explored BMI distribution among the patients and noted that, of the 1261 patients with BMI data available, 40.7% were classified as overweight (25 ≤BMI < 30) and 25.4% as obese (BMI ≥30).

Patient characteristics by race

Median age was significantly different (p < 0.001) with NHO being the youngest (median 58.1 years, range 40.1–83.0) and NHW being the oldest (median 62 years, range 23.2–91.9). Gender distribution was also significantly different among patient race-ethnicity subgroups, with males comprising 67.1% of Hispanics, 59.6% of NHW, 51.8% of NHAA, but only 45.5% of NHO (p = 0.002). We noted that NHAA had the highest proportion of patients classified as obese (27.6%) and NHO had the lowest (12.9%), while NHW had the highest proportion of patients classified as overweight (41.4%) with NHO again having the lowest (29%) (p = 0.018). Among laboratory values evaluated, significant anemia (Hb ≤10 g/dL) was noted in 55.9% NHAA, 49.1% NHO, 44.0% Hispanics, but only in 36.3% NHW (p < 0.001). Similarly, LDH was

### Table 2 Clinical trial and patient characteristics

| Clinical trial characteristic | N = 2896 | Percentage (%) |
|------------------------------|----------|----------------|
| Enrollment year              |          |                |
| 1988–1991                    | 591      | 20.4           |
| 1992–2001                    | 1057     | 36.5           |
| 2002–2011                    | 1248     | 43.1           |
| Novel agent utilized         |          |                |
| Yes                          | 1087     | 37.5           |
| No                           | 1809     | 62.5           |
| Stem cell transplant utilized|          |                |
| Yes                          | 918      | 31.7           |
| No                           | 1978     | 68.3           |
| Duration of treatment        |          |                |
| Fixed duration               | 607      | 21.0           |
| Treatment to progression     | 2289     | 79.0           |
| Patient characteristic       |          |                |
| Race-ethnicity               |          |                |
| Non-Hispanic White           | 2373     | 81.9           |
| Non-Hispanic African Americans| 392     | 13.5           |
| Non-Hispanic other           | 55       | 1.9            |
| Hispanic                     | 76       | 2.6            |
| Age                          |          |                |
| <70 years                    | 2195     | 75.8           |
| ≥70 years                    | 701      | 24.2           |
| Gender                       |          |                |
| Male                         | 1693     | 58.5           |
| Female                       | 1203     | 41.5           |
| International Staging System |          |                |
| ISS I–II                     | 1733     | 71.4           |
| ISS III                      | 694      | 28.6           |
| Missing                      | 469      |                |
| ECOG performance status      |          |                |
| PS = 0                       | 1006     | 35.0           |
| PS > 0                       | 1869     | 65.0           |
| Missing                      | 21       |                |
| Hemoglobin                   |          |                |
| Hb > 10 g/dL                 | 1750     | 60.6           |
| Hb ≤10 g/dL                  | 1136     | 39.4           |
| Missing                      | 10       |                |

*Novel agent = proteasome inhibitors or immunomodulatory drugs

### Table 2 continued

| Patient characteristic | N = 2896 | Percentage (%) |
|------------------------|----------|----------------|
| Lytic lesions          |          |                |
| LL absent              | 1040     | 36.1           |
| LL present             | 1838     | 63.9           |
| Missing                | 18       |                |
| Calcium                |          |                |
| Ca ≤12 mg/dL           | 2759     | 96.2           |
| Ca > 12 mg/dL          | 109      | 3.8            |
| Missing                | 28       |                |
| Creatinine             |          |                |
| Cr <2 mg/dL            | 2238     | 86.8           |
| Cr ≥2 mg/dL            | 340      | 13.2           |
| Missing                | 318      |                |
distributed significantly differently among race-ethnicity subgroups, with NHAA having the highest mean LDH (270.9 U/L) and NHO having the lowest (207.5 U/L) ($p = 0.011$). There were no significant differences among patients for ECOG performance status, ISS stage, presence or absence of lytic bony lesions, bone marrow plasmacytosis, serum calcium, or creatinine level.

Patient participation in the selected clinical trials by race-ethnicity

There were significant differences noted among patients of different racial-ethnic subgroups for all the clinical trial characteristics studied. We noted that, compared to 1988–1991, racial-ethnic minority enrollment in clinical trials increased in 1992–2001, with NHAA increasing from 9.5 to 16.5% and Hispanics increasing from 2.5 to 3.7%. There was a reciprocal decrease noted in NHW enrollment over the same time periods (85.6–78.3%). But in more recent years (2002–2011), minority enrollment has decreased again, with NHAA decreasing to 13% and Hispanics to 1.8% ($p < 0.001$). Majority of patients in all racial-ethnic subgroups were enrolled in clinical trials not involving a novel anti-MM agent. Despite this, NHW had the highest proportion of patients treated on novel therapeutic agent clinical trials (38.5%) while Hispanics had the smallest proportion (25%) ($p = 0.047$). Similarly, majority of patients for all racial-ethnic subgroups were enrolled on clinical trials not involving SCT, but there was a significant difference in the distribution with NHAA having the highest proportion of patients on SCT clinical trials (38%) and NHO the lowest (27.3%) ($p = 0.034$). With respect to fixed duration treatment vs. treatment to progression as well, there were significant differences with 22.1% of NHW but only 5.3% of Hispanics receiving treatment on trials with fixed duration of therapy ($p = 0.001$).

Outcomes by patient characteristics other than race-ethnicity

All the collected demographic and clinical patient characteristics were evaluated for differences in survival in univariate and multivariable models. The study cohort follow-up was censored at 6 years, yielding 2375 progression events and 1782 deaths. Progression-free survival (PFS) was slightly better for females as compared to males (HR 0.92, 95% confidence interval (CI) 0.84, 0.99), while it was significantly worse for those with age ≥70 years (HR 1.17, 95% CI 1.05, 1.31) or an ECOG performance status >0 (HR 1.23, 95% CI 1.12, 1.34). Similarly, patients with ISS stage III (reference ISS stage I–II) had significantly worse PFS (HR 1.20, 95% CI 1.07, 1.34). Among laboratory parameters tested, PFS was significantly worse for patients with Hb ≤10 g/dL (HR 1.22, 95% CI 1.11, 1.33) and for those with serum creatinine ≥2 mg/dL (HR 1.19, 95% CI 1.03, 1.36). PFS was borderline significant for the presence of lytic lesion(s) (HR 1.08, 95% CI 0.99, 1.18) and for patients with serum calcium >12 mg/dL (HR 1.19, 95% CI 0.97, 1.47).

All the same characteristics that were associated with PFS differences were associated with significant differences in overall survival (OS) as well, with a more pronounced effect. These included worse OS associated with male gender (HR for females 0.83, 95% CI 0.75, 0.91, Fig. 1a), age ≥70 years (HR 1.30, 95% CI 1.15, 1.48, Fig. 1b), ECOG performance status >0 (HR 1.46, 95% CI 1.31, 1.62, Fig. 1c), ISS stage III (HR 1.34, 95% CI 1.18, 1.52, Fig. 1d), Hb ≤10 g/dL (HR 1.35, 95% CI 1.22, 1.49, Fig. 1e), and serum creatinine ≥2 mg/dL (HR 1.21, 95% CI 1.03, 1.40, Fig. 1f). In addition, the presence of lytic lesions (HR 1.14, 95% CI 1.03, 1.26, Fig. 1g) and serum calcium >12 mg/dL (HR 1.50, 95% CI 1.20, 1.86, Fig. 1h) were also associated with a significant worsening of median OS.

Outcomes by patient race-ethnicity

Response rates for the primary objectives of clinical trials included were compared among patients of different race-ethnicity groups. There was no statistically significant difference noted for this efficacy analysis ($p = 0.286$) (Fig. 2). Median PFS for the whole study cohort was 2.0 years while the median OS was 4.2 years. Median PFS and OS by race-ethnicity categories are shown in Table 3. Using Hispanics as the reference in the multivariable model, PFS was not noted to be significantly different for any of the race-ethnicity groups ($p = 0.427$) including NHW (HR 1.20, 95% CI 0.92, 1.55), NHAA (HR 1.14, 95% CI 0.86, 1.51), and NHO (HR 1.32, 95% CI 0.88, 1.96) (Fig. 3a). Similarly, OS was not noted to be significantly different ($p = 0.760$) for NHW (HR 1.00, 95% CI 0.75, 1.33), NHAA (HR 0.95, 95% CI 0.70, 1.29), or NHO (HR 1.13, 95% CI 0.73, 1.75) with Hispanics again being the reference (Fig. 3b).

Discussion

Outcomes in MM have improved significantly over the past two decades. Increasing survivorship has led to focus on how the therapeutic advancements may have benefitted various subgroups of MM patients. An important area that deserves focus is patient race-ethnicity. Historically, there has been some work done to understand disease incidence, progression, outcomes, and, to some extent, biologic differences between Caucasians (Whites) and AA, the two largest racial subgroups in the U.S. population. With changing demographic landscape, such an analysis needs to be broadened to include especially Hispanics, the fastest growing racial-ethnic group in the country. Existing data suggests that outcomes among MM patients of different racial-ethnic groups are different and these trends are changing...
Fig. 1 (See legend on next page.)
over time. Causes for this can indeed be multifactorial, but most of the currently available research suggests that access to various therapeutic options may be most important. Clinical trials present a unique opportunity for addressing this question as they contain carefully collected, clinically annotated data, best equipped to perform secondary analyses. The current undertaking involving nine large, national clinical trials in MM conducted at the Cooperative Group level is well positioned for such an analysis.

A higher proportion of patients in our analysis were enrolled in recent years, suggesting increased clinical trial enrollment overall. But we noted a very small proportion of patients in the cohort belonging to racial-ethnic minorities, consistent with other reports of clinical trial enrollment nationally. Similar to a previous report showing increased enrollment of AA patients in clinical trials over time, we noted that, compared to 1988–1991, the number of AA and Hispanics enrolled in clinical trials improved in years 1992–2001. But we also noticed that, in more recent years (2002–2011), this trend actually reversed, and at least in the MM Cooperative Group clinical trials, the enrollment of racial-ethnic minorities decreased. This is contrary to the increasing proportion of racial-ethnic minorities in the U.S. population, representing approximately 30% of MM patients in the U.S. currently. This is a concerning trend despite a requirement by the National Institute of Health that members of minority populations be represented adequately in clinical research. A possible contributor to decreased minority enrollment in the Cooperative Group trials may be their enrollment in other national or regional clinical trials, e.g., those run by pharmaceutical companies or academic institutions. So far, trends of increased minority enrollment in these other settings have not been reported to corroborate this potential hypothesis. Considering that racial minorities may bear the largest burden of cancer in the U.S., their under-representation in clinical trials is a huge source of preventable health-care disparity that needs to be addressed urgently.
We observed that NHW were the ones more commonly enrolled on trials with novel therapeutic agents while Hispanics were least likely to go on to such trials. This could be due to practice patterns, differences in access to certain trials across the country, and even differences in insurance coverage, which is responsible for the non-investigational aspects of a clinical trial. We noted that majority of patients did not get a SCT-based clinical trial, although among those who did, NHAA had the highest proportion of patients. This may again be reflective of differences in practice patterns and geographical availability of trials, since it is known that, overall, racial-ethnic minorities are much less likely to receive SCT for MM10–12.

Racial-ethnic minorities (NHAA and Hispanics) had a younger median age than NHW in our analysis, which has significant implications on outcomes, as age has been noted as an independent prognostic factor in MM3. The gender distribution differences are not necessarily representative of disease incidence by age but may suggest access to and enrollment into clinical trials. Among Hispanics, males were more commonly enrolled as compared to NHAA and NHW. These trends may be helpful in addressing clinical trial enrollment in the future and making sure that access is uniform among demographic subgroups including gender among race-ethnicities.

Obesity has been noted as an independent risk factor for MM in several large analyses21. It has been reported that obesity is a more prevalent problem in racial-ethnic minorities in the U.S., thus possibly putting them at a higher risk of developing MM22,23. While we noted a higher incidence of obesity among the NHAA in our cohort, patient BMI controlling for race-ethnic categories was not associated with differences in PFS or OS. It seems access to effective therapy with clinical trial participation overcame any potential effects of obesity on outcomes. To our knowledge, no prior analysis has looked at patient outcomes in MM by obesity rates and race.

We report significant differences in certain laboratory parameters associated with more aggressive disease, including higher incidence of significant anemia and LDH in NHAA. Other reports have also shown a higher

### Table 3 Progression-free and overall survival by patient race-ethnicity

| Race-ethnicity     | Progression-free survival | Overall survival |
|--------------------|---------------------------|---------------- |
|                    | N (events/patients)       | Median (years)  |
|                    | (95% CI)                  |                |
| Non-Hispanic White | 1960/2373                 | 2.0 (1.9, 2.1) |
| Non-Hispanic African-American | 314/392            | 1.9 (1.7, 2.1) |
| Hispanic           | 60/76                     | 2.7 (1.7, 3.0) |
| Non-Hispanic other | 41/55                     | 1.2 (0.6, 1.9) |
|                    |                           |                 |
|                    | N (events/patients)       | Median (years)  |
|                    | (95% CI)                  |                |
| Non-Hispanic White | 1466/2373                 | 4.2 (4.0, 4.4) |
| Non-Hispanic African-American | 232/392          | 4.3 (3.8, 4.8) |
| Hispanic           | 50/76                     | 4.0 (3.2, 4.9) |
| Non-Hispanic other | 34/55                     | 3.3 (2.3, 4.4) |

CI confidence interval

![Fig. 3 Survival outcomes for patients included in the study by race-ethnicity. a Progression-free survival (PFS) by patient race-ethnicity. b Overall survival (OS) by patient race-ethnicity.](image)
incidence of certain myeloma-defining events, including anemia, in NHAA. Furthermore, in our analysis clinical and demographic parameters, including advanced age, higher disease stage, poor performance status, presence of lytic bony lesions, significant anemia, hypercalcaemia and renal dysfunction, were associated with worse outcomes, similar to prior reports. Our observation is important, as, despite adverse prognostic markers in certain racial-ethnic groups, patients had similar response rates and survival, underscoring the importance of access to appropriate therapeutic options, e.g., participation in clinical trials. To this end, we report that there were no differences in objective response rates, PFS, or OS by race-ethnicity across the nine included national clinical trials. While there was heterogeneity in the clinical trials included, the proportion of minority enrollment was similar across various trials, rendering validity to this unique observation. This is in accordance with smaller previous reports that have evaluated single-institution or single-trial data. We confirm these findings on a larger scale spanning many more years of patient care.

We report the analysis from a large, prospectively collected national data, which shows low clinical trial accrual for racial-ethnic minorities. Nevertheless, despite heterogeneity in patient characteristics including some poor-risk features, patients from racial-ethnic minorities had similar outcomes to NHW, the most numerous group. This underscores the therapeutic benefit that evidence-based and novel treatment options, typically offered in prevalent clinical trials, bring to patients. Ongoing efforts regarding improving clinical trial accrual in the U.S., especially among racial-ethnic minorities, need to be strengthened further, which may require a concerted focus from patients, health-care and advocacy groups as well as political will.

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Conflict of interest
The authors declare that they have no conflict of interest.

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