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Comparisons of the Response of Chemo/BMT Treatment and Survival Outcomes between African American and Caucasian Patients with Multiple Myeloma

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Zheyu Hu

Abstract:

This study aimed to investigate the racial disparity in patients' response to chemotherapy / bone marrow transplantation (BMT) and the survival outcome in multiple myeloma (MM) patients. A total of 370 white MM patients and 370 African American (AA) patients were treated with chemotherapy and BMT. The demographic and clinical information were recorded. Univariate and multivariate logistic regression analysis were performed to evaluate the racial disparity in pretransplant response, BMT response, and the improvement of response after BMT. The survivor functions for progression free survival (PFS) analysis and overall survival (OS) analysis in white and AA patients were estimated by the method of Kaplan and Meier. The log-rank test was used to test the difference. A COX model was employed to estimate the univariate effect of race and all other variables on PFS or OS as well as the adjusted effects of race by other factors on PFS or OS. We found that AA patients were younger with more female and have lower albumin and higher quantitated IgG level. AA patients were less likely to have anemia and hypertension, buy more likely to have lytic bone lesion. The usage of Melphalan, mobilization with growth factor and thalidomide maintenance were significantly higher in AA patients, while the usage of thalidomide and lenalidomide maintenance were significantly lower among them. As for the treatment response, we found that there was no significant racial disparity in pre-transplant response, treatment response at day 100 after BMT, and response improvement. In PFS analysis, we found that the hazard rate of progression or death among AA patients was significantly lower (only 0.783 [95% CI: 0.632 - 0.9696] folds) than white patients. ISS stage, the presence of lytic bone lesion, hypercalcemia, anemia, renal insufficiency, thalidomide, dexamethasone, etoposide, cytoxytan, carboplatin, growth factor mobilization and thalidomide maintenance were also shown to be significantly risk factors of PFS. We did not find racial disparity in OS. But, ISS stage, cytogenetics, the presence of lytic bone lesion, hypercalcemia, anemia, DM, renal insufficiency, velcade, thalidomide, dexamethasone, doxorubicin, cytoxytan, carboplatin, etoposide and bortezomib maintenance were found to be risk factors of OS.

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Chapter 1

Introduction

Definition and pathological characters of Multiple Myeloma

Multiple myeloma (MM) is a kind of malignant plasma cell disease, originated from plasmacytes in bone marrow. Since plasmacytes are formed at the final stage in B lymphocytes maturity process, so world health organization (WHO) defines multiple myeloma as a specific kind of B cell lymphoma.

The main pathological character of MM is the abnormal proliferation of bone marrow plasmacytes (myeloma cells) along with the over-generation of monoclonal immunoglobulin or light-chain (M protein). Based on the immunoglobulin type that generated by myeloma cells, MM is categorized into IgG (50-60%), IgD, IgA, IgE (most rare type), IgM, light-chain, double-clonal, and non-secretory type. MM is also characterized by several other features, including low blood cells and anemia, lytic bone lesion and hypercalcemia, infections (because normal anti-infection antibody generation is prohibited by malignant plasmacytes), renal damage (attacked by abnormal antibody), monoclonal gammopathy and light chain amyloidosis. Although monoclonal gammopathy of undetermined significance (MGUS) doesn't cause clinical symptoms like MM does, some people with MGUS will eventually develop MM. MM is consistently preceded by MGUS (Landgren et al., 2009). Based on pathological features, MM is also classified into three categories: MGUS, asymptomatic myeloma (further subdivided into smoldering myeloma and indolent myeloma) and symptomatic myeloma. In this study,

we focused on symptomatic myeloma, and MGUS was considered as a historical precursor disease.

Epidemiology and racial disparity of Multiple Myeloma

MM accounts for approximately 1% of all cancers and 10% of hematologic malignancies worldwide. It is also the second most common hematological malignancy in United States (US), with an estimated 89,658 people living with MM in US in 2012. The American Cancer Society (ACS) has estimated 26,850 new cancer cases in the US in 2015, with an estimated 11,240 deaths (Siegel, Miller, & Jemal, 2015). The incidence rate of MM increases to 6.3 per 100,000 person year worldwide. Most patients are older than 40 years old. More than 60% of the patients diagnosed after the age of 65. Male and female ratio is 1.6 versus 1. The 5-years surviving rate in 2005 to 2011 is 46.6%. The number of deaths was 3.3 per 100,000 men and women per year (age-adjusted and based on 2008-2012 cases and deaths) (NCI Surveillance, 2016).

The incidence rate of MM has racial disparity. African Americans (AA) have the highest incidence rate, twice as common in AA as it occurs in White Americans. The incidence rate of MM in AA is 15.1 for males and 11.2 for females, while the incidence rate in white is 7.5 for males and 4.5 for females (SEER 2008-2012) (NCI Surveillance, 2016). Based on a single center study in Greenebaum Cancer Center, black MM patients are significantly younger than white patients (median age, 54 years vs 59 years; $p<.0001$), and are more frequently presented with anemia ($p = 0.04$) (Bhatnagar et al., 2015). Based on a cohort study in 2013, except for a significantly lower frequency of IgH translocations (40% vs 52%; $p = 0.032$) in AA patients, the genetic profiles and

frequency differences of somatic copy number aberrations are similar between AA and white MM patients (Baker et al., 2013). However, some other reports suggest that the inherited predisposition to MM might be part of the explanation for observed racial disparities in the incidence of MM (Morgan et al., 2014). A multi-center study suggests significant racial difference in cytogenetic abnormalities: MM in blacks is associated with excessive prevalence of either the trisomic (hyperdiploid) form or an IgH translocation besides t(11;14) or t(4;14) (Greenberg et al., 2015).

MGUS is detectable in 3-5% of individuals aged 50 years or older in European populations (Weiss, Abadie, Verma, Howard, & Kuehl, 2009) and has around annual risk of 1% to progress to MM. The incidence of MGUS among AA is reported to be 2-fold compared with whites. Obesity, black race, and increasing age are found to be independently associated with a high risk of MGUS (Orgel et al., 2014). Hyperphosphorylated paratarg-7 (P-7) is the first molecularly defined inherited risk factor associated for MGUS and MM (Weiss et al., 2011). By using isoelectric focusing and ELISA methods, P-7 is observed in 37.0% AA, 16.7% European and 4.0% Japanese MGUS/MM patients, while it is found in 11.0% AA, 1.5% European and 0.4% Japanese healthy controls ($p < 0.001$) (Zwick et al., 2014). P-7 carriers are most prevalent among AA and the high prevalence of P-7 carriers among AA patients emphasizes a predominant role of this genetic factor in the pathogenesis of these diseases. Except for P-7, other risk genes associated MGUS / MM include DNA methyltransferase 3 alpha (DNMT3A), CCDN1 (t11;14), CDCA7AL (cell division cycle associated 7-like), CCND1 (t(11;14)(q13;q32) translocation), etc (Broderick et al., 2012; Chubb et al., 2013; Weinhold et al., 2013). These studies identified SNPs at chromosomes 2p23.3, 3p22.1,

3q26.2, 6p21.33, 7p15.3, 17p11.2 and 22q13.1 robustly associated with risk of MM (Morgan, et al., 2014).

Diagnosis, Staging and treatment of MM

The diagnostic workup for MM patients include a history and physical examination, blood studies and biological assessments of complete blood cell count with differential platelet counts, blood urea nitrogen (BUN), serum creatinine, serum calcium, albumin, lactate dehydrogenase (LDH), and beta-2 microglobulin. The monoclonal protein (M-protein) component in serum and urine is also detected for diagnosis. Serum analysis includes quantitative immunoglobulin levels of different types of antibodies (IgG, IgA and IgM). Bone marrow studies at initial diagnosis include chromosome analysis by conventional karyotyping (cytogenetics) and fluorescence in situ hybridization (FISH). The International Myeloma Working Group (IMWG) recently updated the diagnosis of MM, including biomarkers plus CRAB features (common symptoms of multiple myeloma: C = Calcium [>11.5 mg/dl], R = Renal failure [creatinine > 2 mg/dl or creatinine clearance < 40 mL/min], A = Anemia [2 g/dl < hemoglobin < 10g/dl], B = Bone lesions) (Rajkumar et al., 2014). The MM defining biomarkers identified by the IMWG include one or more of the following: >60% clonal plasma cells in the bone marrow, involved / uninvolved free light chain (FLC) ratio≥ 100 with the involved FLC ≥ 100 mg/L, and more than one focal lesion in bone imaging (PET-CT or MRI). The international staging system (ISS) is based on beta 2-microglobulin (β_2-M) and albumin blood level and now commonly used (Greipp et al., 2005). In stage I, serum beta-2 microglobulin is less than 3.5 mg/L and serum albumin is greater or equal to 3.5 g/dL

mg/L; in stage III, serum beta-2 microglobulin is greater or equal to 5.5 mg/L; stage II is in the middle level. The Durie-Salmon Staging System is an older staging system that is determined by hemoglobin blood level, calcium blood level, the number of bone lesions, M protein production rate, and the renal function (Durie & Salmon, 1975).

Primary therapy for symptomatic MM includes chemotherapy and bone marrow transplantation. Since regimens with stem cell toxins (notably melphalan) should be avoided in patients who are potential candidates for bone marrow transplantation (BMT), so the first step in evaluating patients with advanced MM is to determine whether they are candidates for high-dose therapy and transplantation. BMT is a potentially curative therapy for kinds of hematological disorders (Blume KG, 2004). However, the mortality associated with BMT remains significant. So, the decision of BMT therapy is not simply depend on diagnosis, instead it is a complex process intricately dependent on a serial of variables, including age, disease and remission status, physiological status, psychosocial, psychological, financial and caregiver considerations (Hamadani, Craig, Awan, & Devine, 2010). Even old age and renal dysfunction are not absolute contra-indications to BMT, but appropriate adjunctive measures should be used to avoid early complications that may compromise BMT outcome.

Preferred regimens for transplant candidates include: Bortezomib / dexamethasone (VD), Bortezomib / cyclophosphamide / dexamethasone (VCD), Bortezomib / thalidomide / dexamethasone (VTD), Bortezomib / doxorubincin / dexamethasone (VDD), Bortezomib / revlimide (lenalidomide) / dexamethasone (VRD), Revlimide / dexamethasone (RD) (Harousseau JL, 2007; Kumar et al., 2012; Rajkumar et al., 2010; Reeder et al., 2009; Richardson et al., 2010). Other regimens include thalidomide /

dexamethasone (TD), liposomal doxorubincin / vincristine / dexamethasone (DVD), etc (Rajkumar et al., 2005).

Before BMT, IMWG recommend an early mobilization of stem cells, preferably within the first 4 cycles of initial chemotherapy, especially for patients treated with RD or VRD, because a decrease in CD34-positive cells collected after prolonged revlimid treatment has been reported (Paripati et al., 2008). In majority of patients who undergo autologous stem cell transplant (ASCT), stem cells are collected from the peripheral blood following mobilization using growth factor with or without preceding chemotherapy (Kumar et al., 2009). Chemo-mobilization could overcome the inability of stem cell collection (Mark et al., 2008). Moreover, when conventional mobilization methods fail, the addition of chemokine receptor type 4 (CXCR4) inhibitor plerixafor could help facilitate the successful stem cell harvest (Nademanee et al., 2012).

Even high-dose chemotherapy is followed by successful BMT, MM recurrence occurs almost universally in patients who do not receive post-transplantation treatment. Maintenance therapy refers to a planned treatment that is effective, well-tolerated with manageable toxicities, simple to administer and can be given for an extended period of time. Maintenance can improve outcomes after BMT (Landau & Giralt, 2014). Preferred maintenance regimens include bortizomib, revlimid, and thalidomide. Thalidomide maintenance after BMT is shown to improve the quality of response and increase progression free survival (PFS) and overall survival (OS), but the side-effects are neuropathy and fatigue (Ludwig et al., 2012). Revlimid maintenance has much favorable side-effect and is capable to improve 3-year OS (Shimizu, 2014).

Based on the international uniform response criteria for MM (Durie et al., 2006), the treatment response were divided into six categories, complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), progress and relapse.

Concerning to the racial disparity in treatment response, the overall treatment response to chemotherapy induction has been shown to be similar between AA and white MM patients, but the deeper responses were observed in more white patients than black patients who receive immunomodulatory drug-based therapy (thalidomide analogues) ($p=0.02$). In addition, the referral for BMT is also significantly delayed in AA compared to whites (median, 1.3 years vs 0.9 years; $p = .003$) (Bhatnagar, et al., 2015).

Prognostic biomarkers for Multiple Myeloma

As for the biomarkers for MM, researchers have suggested that a panel of indicators is poor prognosis predictors in newly diagnosed MM patients. These indicators include cytogenetic abnormalities, such as presence of hypodiploidy, t(4;14), t(14;16), del(17p) and del(13), serum β_2-microglobulin levels greater than 2.5 mg/L, an elevated plasma cell, and detection of circulating plasma cells, (Avet-Loiseau et al., 2007; Kyle & Rajkumar, 2009; Nowakowski et al., 2005).

Besides, high heparanase and shed sydecan-1 levels in MM bone marrow microenvironment can elevate vascular endothelial growth factor (VEGF) level and are associated with angiogenesis and poor prognosis (Purushothaman et al., 2010). Blood soluble programmed death-ligand 1 (sPD-L1) is a cell cycle checkpoint-relevant protein. It has been reported to be a valuable biomarker for predicting treatment response and an independent prognostic factor for PFS and survival outcomes in MM patients. Based on

81 newly diagnosed MM patients, Wang L et al reported that the response rate to treatment was higher in low sPD-L1 patients than in high sPD-L1 patients (Wang et al., 2015). Moreover, based on 108 MM patients and 56 healthy donors, the decreased expression of miR-19a in MM is reported to be positively correlated with advanced ISS stage, del(13q14) and 1q21 amplification, and shorter PFS and OS. Although miR-19a levels predicts a poor prognosis, patients with low miR-19a level have an improved response to Bortezomib compared to those with high miR-19a profile, and patients with downregulated miR-19a experienced a significantly extended survival upon Bortezomib-based therapy (Hao et al., 2015). MM is also characterized by immune deregulation. Interleukin-22 (IL-22) has been shown to be higher in active and advanced-stage MM patients, compared to both health control and patients in remission. It is correlated with β_2-M, and may represent the inflammatory element of the disease (Tsirakis et al., 2015). Programmed cell death-1 (PD-1) is enriched on T cells in MM patients to mediate tumor escape from immune control in animal models, which is related to immune dysfunction in MM patients (Hallett, Jing, Drobyski, & Johnson, 2011). In addition, gender also plays a role in clinical outcome. Females are reported to have a higher prevalence of bone lesions associated with genetic events, such as t(14; 16) and +1q, which may be a poor predictor and adversely affect clinical outcome (Boyd et al., 2011).

As for the racial difference in MM biomarkers, immunoglobulin G isotype and risk cytogenetic markers are significanatly higher in AA (Bhatnagar, et al., 2015). Moreover, in MGUS patients, the M-protein isotype profile in blacks are 81% IgG, 13% IgA, 2% IgM, and 4% biclonal, compared to 70%, 12%, 16%, and 2% in whites, respectively, ($p <$

0.0005). The median M-protein concentration for blacks was 0.44 gm/dL, compared to 1.2 gm/dl in whites (Landgren & Weiss, 2009).

Recurrence and survival in multiple myeloma

With novel agents, OS in MM patients has improved over last decade. As demonstrated by the Surveillance, Epidemiology, and End Results Program (SEER) of the US National Cancer Institute, the 5-year surviving rate is 46.6% in 2005 to 2011 period (NCI Surveillance, 2016). Based on SEER data of 40,294 MM patients in the years from 1973 to 2003, Asian/Pacific Islander race was associated with an improved OS while American Indian/Alaska Native race was associated with a decreased OS. In addition, multivariate analysis did not reveal statistically significant differences in OS between black and white patients (Kaya et al., 2012). Based on a retrospective review for patients who achieved CR from January 1990 to December 2002 in MD Anderson Cancer Center, multivariate analysis demonstrates that high tumor mass at diagnosis is a predictor for significantly shorter remission duration and poor outcome (Qazilbash et al., 2006). Most MM patients even achieving CR eventually relapse or become refractory to current treatment. In high-risk patients with increased creatinine > 2mg/dL, Bortezomib can significantly improve PFS from a median of 13 months to 30 months and OS from a median of 21 months to 54 months (Sonneveld et al., 2012). A review of long-term outcome of autologous transplantation finds that tandem transplantations with a longer post-relapse survival is superior to both single transplantation and standard therapies (Barlogie et al., 2010).

The major problem in MM treatment is drug resistance (Yang & Lin, 2015). The possible mechanisms of drug resistance include multiple drug resistance (MDR) gene polymorphism and p-glycoprotein (g-P) overexpression, micro-environmental changes (cell adhesion and activation of cytokine-related anti-apoptosis pathways), and selected CD34+CD138+B7-H1+CD19− plasma cell accumulation after treatment (Kuranda et al., 2010). Genetic examination suggests that the incidence of 1q21 amplification and t(4;14) unbalanced translocation is higher in relapsed patients than in newly diagnosed patients (Hanamura et al., 2006). Clonal evolution such as hyper-expression of the proteasome-related gene is related to chromosome 1q21 amplification.

As for the racial disparity, AA has excessive mortality hazard ratio of 1.20 (95% CI: 1.09 - 1.33) compared to non-Hispanic Whites in 2006 - 2009 (Pulte, Redaniel, Brenner, Jansen, & Jeffreys, 2014). Based on a single center study, the OS from BMT has been shown to be similar for AA and White patients. However, OS from diagnosis was significantly longer among black individuals compared to white patients (median, 7.7 years vs 6.1 years; $p = 0.03$). Maintenance therapy was found to positively impact PFS but not OS, irrespective of race (Bhatnagar, et al., 2015).

Study goal

Even the racial disparity has been demonstrated in MM patients, no comprehensive analysis has been performed to provide a whole picture about how clinical and pathological indicators affect the different treatment response and OS / PFS between AA and white patients. In this study, to identify the factors that significantly affect treatment response, OS and PFS in AA and white MM patients, we recruit 370 AA and 370 white

MM patients in Emory University Winship Cancer Institute. Treatment responses were analyzed in AA and white patients and the racial disparity was adjusted by other clinical and pathological variables in multivariate logistic models. In survival analysis, we identified the significant variables that affected OS or PFS in AA and white patients. The proportional hazard ratio of race adjusted for significant variables was obtained in our study.

Chapter II

Methods

Study population and clinical data collection

Study population and data collection referred to the paper of Carsten Zwick (Zwick, et al., 2014). Equal number (n=370) of consecutive AA and white patients with MM in Emory University Winship Cancer Institute were included. Written informed consent was obtained from all patients. All patients with a diagnosis of multiple myeloma identified through the tumor registry records and from hematology clinic were eligible for the study. The demographic and clinical information were recorded, including age, sex, MM stage, clinical symptoms, complications, cytogenetics, laboratory indicators, immunoglobulin subtypes, chemotherapy regimens, treatment response, BMT mobilization, maintenance, BMT response, treatment toxicity, and survival time.

Patients with ISS stage 0 to 3 were included in this study. Stage 0 is the smoldering myeloma (asymptomatic myeloma). Based on chromosome abnormality, cytogenetics risk were divided into four classes: high (presence of del(17p) and translocation t(4;14) and / or translocation t(14;16)), standard , low / intermediate, and normal. The laboratory indicators include M-protein spike value, kappa level, lambda level, plasma K/L (kappa and lambda ratio), β_2-microglobulin, albumin, creatinine, immunoglobulin subtypes and their quantitated levels. Associated diseases and clinical symptoms include plasmacytoma, MGUS, presence of lytic lesions, hypercalcemia, amyloidosis, anemia, auto-immunological disease, diabetes mellitus (DM), deep vein thrombosis (DVT), high-cholesterol, hypertension (HTN), renal insufficiency, and other cancers. As for the chemotherapy, number of lines of chemotherapy was calculated and the last

chemotherapy regimen for each patient was recorded. The chemo-agents, mobilization agents and maintenance agents that each patient used were also recorded. The treatment toxicities, including infection, gastric and intestine reaction, neuropathy, neutropenia, rash and thrombocytopenia, are also included. We also include the response variables, such as pre-transplantation response, response at 100 days after BMT and response improvement after BMT. As for the survival relevant variables, status (death or alive), days from diagnosis to transplant, days from diagnosis to relapse, days from BMT to relapse and days from BMT to last contact were also kept in our datasets.

Statistical Analyses

The main purpose of this study is to investigate the racial disparity of clinical indicators that were described above. We also assessed the response difference between AA and white patients to chemotherapy and BMT. Then, we evaluated the OS and PSF difference between AA and white MM patients. The confounders that might affect the racial disparities were also examined and determined in this study.

Descriptive analysis: The clinical and pathological characteristics are summarized and compared between AA patients and white patients. Laboratory indicators, such as M spike value, kappa, lambda, plasma k/l ratio, β_2 microglobulin, albumin, creatinine, and quantitated immunoglobulin level are continuous variable and compared with *student-t* test. Other variables, such as gender, ISS stage, cytogenetics, immunoglobulin subtypes, associated disease or symptoms, chemotherapy and usage of chemo-agents, BMT mobilization, and maintenance after BMT, toxicity, and treatment response are categorical variable and compared with Chi-square test.

Univariate logistic regression analysis: Since the overall transplant response (either pre-transplant response or day 100 after BMT response) were divided into two categories, responded (CR+VGPR+PR) and not-responded (SD + progression + relapse). Logistic regression analysis was employed to test the significance across different strata of each independent categorical variable. We also evaluated effect of each continuous variable on the response outcome.

Multivariate logistic regression analysis: After univariate logistic regression analysis, variables that significantly affect the response outcome were selected (significance level α=0.05). Then, multivariate logistic regression approach was used to estimate the adjusted relationship between treatment response and race after adjustment for all other significant factors.

Survival analysis: Time of OS was calculated as the time from diagnosis to death or last contact. Time of PFS was calculated as the time from disease diagnosed to disease progression date, death date, or last contact whichever comes first. The survivor functions for PFS or OS were estimated by the method of Kaplan and Meier (Kalbfleisch JD, 1980). The log-rank test was used to test the difference in the overall PFS or OS between different groups stratified by the factors. A COX model (Cox, D. R.) (Cox, 1972) was employed to estimate the univariate effect of race and all other variables on PFS or OS as well as the adjusted effects of other factors on PFS or OS.

The SAS statistical package (SAS Institute, Inc., Cary, North Carolina) is used for all data managements and analyses.

Chapter III

Results

Demographic and Clinical characteristics

370 AA and 370 white MM patients were enrolled in this study. As shown in table 1A, the mean (± SD) age of AA and white patients were 54.91 (± 9.60) and 58.88 (± 8.29), respectively (p-value=0.0001). Among 370 AA patients, 172 (46.49%) were males and 198 (53.51%) were females, compared with 217 (58.56%) males and 153 (41.35%) females among 370 white patients (p=0.0009). As for the stage and cytogenetics, there were no significant differences between AA and white patients (p=0.392 and 0.776, respectively).

For the racial difference in lab indicators and immunoglobulin subtypes, albumin level was significantly different between AA and white patients (p<0.0001), with a mean (±SD) level of 3.40 (±0.79) and 3.66 (± 0.71) in AA and white, respectively. Quantitated immunoglobulin IgG level was also higher in AA with mean (±SD) of 3393.8 (±3100.2), compared to white patients with mean (±SD) of 2627 (±2634.8) (p = 0.0146). M spike value, kappa, lambda, β_2 microglobulin, creatinine, plasma kappa / lambda ratio and quantitated immunoglobulin IgM and IgA levels were not significantly different between two racial groups. The immunoglobulin subtypes (IgG, IgA, IgM and IgD) was almost equal between AA and white.

Concerning to the associated diseases or symptoms, the frequency of anemia was significantly higher in white patients than AA patients (n=82 [29.75%] vs n=29 [11.37%], p<0.001). Hypertension was another associated disease that occurred more frequently in white patients compared to AA patients (n=243 [65.68%] vs n=198 [53.51%], p<0.001).

However, the presence of lytic bone lesion was more often in AAthan white patients (n=175 [47.3%] vs n=140 [37.84%], p=0.009). Hypertension, the presence of lytic bone lesion, MGUS, diabetes mellitus (DM), high-cholesterol, high-cholesterol and other cancer were marginally significantly different between AA and white patients. MGUS was marginally higher in AA than white patients (n=333 [90%] vs n=318 [85.95%], p= 0.09). The existence of other cancer was also marginally more frequent in AA than white patients (n=357 [96.49%] vs n=347 [93.78%], p=0.087). DM and high-cholesterol happened marginally more frequently in white patients (n = 331 [89.46%] and 333 [90%], respectively), compared to AA patients (the same n = 316 [85.41%] for both DM and high-cholesterol), with p-values of 0.069 for DM and 0.057 for high-cholesterol. Other clinical symptoms or associated diseases, including plasmacytoma, hyperclacemia, amyloidosis, auto-immunological disease, B-cell neoplasm, DVT and renal failure, were almost equal in AA and white MM patients.

For the induction chemotherapy prior to BMT, both the number of chemotherapy lines and the last chemotherapy regimens before BMT were not significantly different between AA and white MM patients (p-value = 0.5204 and 0.326, respectively). Melphalan was more frequently used in white patients than AA patients (354 [95.68%] vs 299 [80.81%], p<0.001), while thalidomide was more used in AA patients than white MM patients (237 [64.05%] vs 209 [56.49%], p=0.035). Besides thalidomide, the usage of dexamethasome was marginally higher in AA patients compared to white patients (21 [5.68%] vs 11[2.97%], p=0.071). The usage of cytoxytan was marginally lower in AA patients compared to white MM patients (339 [91.62%] vs 351 [94.86%], p=0.079).

For BMT mobilization and conditioning, the mobilization with growth factor was significantly higher in AA patients than white MM patients (n=60 [19.35%] vs. 3 [0.88%], p<0.001). The usage of cytoxan mobilization, mozobil mobilization, melphalan conditioning, VTDPACE/DCEP/cyclophosphamide/fludarabine conditioning and velcade (Bortezomib) conditioning were almost the same between two racial groups of patients. As for the maintenance after BMT, AA patients were marginally lower frequently treated with maintenance agents after BMT compared to white patients (100 [34.72%] for AA vs 121 [41.58%] for white) with a p-value of 0.089. Significantly more white patients were treated with lenalidomide (revlimide) maintenance (208 [63.03%]) than AA patients (159 [49.84%]), with a p-value of less than 0.001. But thalidomide was more used for maintenance after BMT in AA compared to white patients (303 [94.98%] vs 297 [90%], p = 0.016). No significant differences were found in velcade usage and clinical trial or other drug usage in maintenance between AA and white MM patients. In addition, the occurrence of treatment toxicities, including infection, GI reaction, neuropathy, neutropenia, rash and thrombocytopenia, was almost equal in AA and white MM patients.

Racial disparity in chemotherapy and BMT response

To investigate the effect of race on pre-transplant response, logistic regression was applied. As shown in table 2A, the odds of being responded to treatment before BMT among AA patients was 1.452 (95% CI: 0.905, 2.329) fold higher than the odds of being responded before BMT among white patients. In table 3A, by using multivariate logistic regression, we found that gender, diabetes, the use of cytoxytan, carboplatin, and clinical

trial drug were significant confounders that related to racial disparity in the pre-transplant response.

We then use logistic regression to investigate radial disparity in treatment response at 100 days after transplantation. As shown in table 2B, the odds of being responded to treatment before BMT among AA patients was 0.776 (95% CI: 0.424, 1.419) fold compared white patients. In multivariate logistic regression analysis, we found that the usage of cytoxytan was significant confounder that affected the racial disparity in post-transplant response at day 100 (Table 3B).

To further evaluate the effect of BMT on racial difference in treatment response, we investigate the clinical markers that associated with the response improvement after BMT. As shown in table 2C, the odds of response improvement among AA patients was 0.785 (95% CI: 0.510, 1.208) fold compared to the odds of response improvement among white patients. In multivariate logistic regression model, the last chemotherapy regimen before BMT was a significant confounder along with the racial disparity (Table 3C).

Analysis of progression free survival in MM patients

Univariate Cox proportional hazard model were used to analyze PFS, where PFS was defined as the time from diagnosis until disease progression or death. The significant laboratory and clinical factors were identified by Log-rank test and Wald test. The hazard rate of disease progression or death in AA was significantly lower (HR: 0.783, 95% CI: 0.632 - 0.969, p=0.0244), compared to white patients (Figure 1 and Table 4A). As for the stage_iss, the hazard rate of progression or death in patients with stage 1 was significantly lower (HR: 0.532, 95% CI: 0.380 - 0.744, p=0.0002) compared to patients in

stage 3. For cytogenetics, we found that the hazard rate of patients with high-risk, standard-risk and low/intermediate risk were 1.439 (95% CI: 0.956-2.165), 1.841 (95% CI: 1.170 - 2.897), and 1.260 (95% CI: 0.853 - 1.860) folds, respectively, compared to patients with normal cytogenetics ($p = 0.0438$). Then, we evaluated the lab indicators and found that lambda, β2 microglobulin, albumin, quantitated-IgA, kappa at day 100 after BMT and plasma k/l at day 100 after BMT significantly affected PFS with $p<0.05$.

As for the related clinical symptoms or diseases, we found that the hazard rate of progression or death in patients with the presence of lytic lesion, hypercalcemia, anemia or renal insufficiency was 1.346 (95% CI: 1.084 - 1.672), 2.104 (95% CI: 1.588 - 2.840), 1.725 (95% CI: 1.238 - 2.404) or 1.330 (95% CI: 1.030 - 1.717) folds, respectively, compared to patients without such symptoms or diseases ($p< 0.05$). For the chemotherapy, we found that the number of lines prior to transplantation was significant, the hazard rate of progression or death in patients with 1 to 5 lines of chemotherapy was 2.019 to 4.059 folds higher compared to patients with 6 lines of chemotherapy ($p =0.01$). As for the individual chemo-agents, we found that the hazard rates of progression or death in patients with thalidomide, dexamethasone, etoposide, cytoxytan or carboplantin treatment were 1.450, 2.66, 1.81, 1.56, 1.95 folds higher than patients without such treatment ($p<0.05$). The hazard rate of progression or death in patients with growth factor mobilization was 2.11 (95% CI: 1.08 - 4.10) folds higher compared to patients without growth factor mobilization ($p = 0.025$). Moreover, the hazard rate of progression or death among patients with thalidomide maintenance was also significant higher (HR=1.43, 95% CI: 1.01 - 2.02) compared to patients without such maintenance ($p =0.042$). Compared to patients with normal immunoglobulin subtype at day 100 after treatment,

the hazard rate of progression or death in patients with IgA was 1.822 (95% CI: 1.184 - 2.805) folds higher (p=0.014 for the immunoglobulin subtype). In multivariate progression free analysis, we found that thalidomide was a significant confounder that affected the racial disparity in PFS (table 4B)

Overall survival analysis in MM patients

Univariate Cox proportional hazard model analyses were performed to analyze the effect of clinical factors on OS in MM patients (Table 5A). Significant factors were identified by Log-rank test and Wald test. The hazard rate of death in AA was almost equal to white. The hazard rate of death in stage 3 was significantly higher than stage 1 and 2 ($p<0.0001$). As for the associated diseases and symptoms, the hazard rate of death in patients with the presence of lytic lesion was 1.347 (95% CI: 1.038, 1.748) fold compared to patients without lytic bone lesion. Also, the hazard rates of death were significantly higher in the patients with hypercalcemia, anemia, DM, or renal insufficiency compared to the patients without these diseases or symptoms. For the chemotherapy, both the number of lines of chemotherapy and the last chemotherapy before BMT had an overall significant effect on OS. The hazard rates of death in patients with velcade, thalidomide, dexamethasome, doxurubicin, cytoxytan, carboplatin or etoposide treatment were 1.37 (95% CI: 1.01, 1.86), 1.29 (95% CI: 1.00, 1.67), 2.46 (95% CI: 1.20, 5.04), 1.46 (95% CI: 0.57, 2.19), 2.23 (95% CI: 1.52, 3.27), 2.48 (95% CI: 1.76, 3.51) and 2.31 (95% CI: 1.64, 3.24) folds, respectively, compared to patients without treatment.

Concerning to the mobilization and maintenance after BMT, the hazard rate of death in patients with growth factor mobilization were 1.96 (95% CI: 0.87, 4.44) folds higher compared to patients without growth factor mobilization. Also, the hazard rate of death in patient with Bortezomib maintenance was 2.04 (95% CI: 1.42, 2.92) times of hazard rate of death in patients without Bortezomib maintenance. Besides these treatment-related factors, the immunoglobulin subtype after BMT treatment also had marginally significant effect on OS (p=0.054). Compared to patients with normal immunoglobulin, the hazard rate of death in patients with IgA was 1.94 (95% CI: 1.18 - 3.19) folds higher.

Multivariate Cox proportional hazard regression model was performed to analyze OS of in MM patients, by enforcing race in the model with the above significant and marginally significant variables. Except race, stage_iss, hypercalcemia and cytogenesis were retained in the multivariate model for OS. The overall log-rank p-value was 0.0041 (Table 5B).

Chapter IV

Discussion

In this study, we found that AA patients were younger than white patients. While 53.51% AA patients were female, only 41.35% white patients were female. Compared to white patients, AA patients have significantly lower albumin level and higher quantitated IgG level. Moreover, the frequency of anemia and hypertension were significantly higher in white patients, while the presence of lytic bone lesion was significantly lower in white patients. The usage of melphalan, mobilization with growth factor and thalidomide maintenance were significantly higher in AA patients, while the usage of thalidomide and lenalidomide maintenance were significantly lower in AA patients. Then, we found that there was no significant racial disparity in pre-transplant response, treatment response at day 100 after BMT, and response improvement (Table 2A-2C). In PFS analysis, we found that the hazard rate of progression or death among AA patients was significantly lower compare to the hazard rate of progression or death among white patients (Figure 1 and Table 4A). Also, patients with lower ISS stage have significantly lower hazard rate of progression or death compared with those with ISS stage 3. The hazard rates of progression or death in patients with the presence of lytic bone lesion, hypercalcemia, anemia, renal insufficiency, thalidomide, dexamethasone, etoposide, cytoxytan, carboplatin, growth factor mobilization or thalidomide maintenance were significantly higher than the hazard rate of progression or death among patients without above clinical characteristics. As for the last chemotherapy prior to BMT and number of lines of chemotherapy prior to BMT, they both could individually affect the PFS outcome.

Moreover, the hazard rate of progression or death among patients with response improvement after BMT were significantly lower than that among patients without response improvement (HR= 0.732, 95% CI: 0.577 - 0.930). Compared to patients with normal immunoglobulin at day 100 after BMT, the hazard rate of progression or death among patients with abnormal immunoglobulin subtypes was significantly higher (p = 0.0142). As for OS, we found that compared to patients in stage 3, hazard rate of death among patients with lower ISS stage was significantly lower. The hazard rates of death among patients with higher cytogenetics, the presence of lytic bone lesion, hypercalcemia, anemia, DM, renal insufficiency, velcade, thalidomide, dexamethasone, doxorubicin, cytoxytan, carboplatin, etoposide or Bortezomib maintenance were significantly higher than the hazard rate of death among patients with normal cytogenetics or without the above clinical characteristics. As for the number of lines prior chemotherapy and last chemotherapy regimen before BMT, the hazard rate of death among patients with 1-5 lines of chemotherapy was significantly higher than the hazard rate of death among patients with 6 lines of chemotherapy regimen. Multivariate analysis suggested a model with race, stage-ISS, hypercalcemia and cytogenesis (Table 5B).

Previous literatures have demonstrated that AA have a higher incidence rate to get MM than white (NCI Surveillance, 2016) due to genetic racial disparity. Compared to white patients, AA patients are reported to be younger; Also, AA are more frequently presented with anemia, more of the immunoglobulin G isotype, and have higher cytogenetic risk (Bhatnagar, et al., 2015). Here, we showed that AA patients were different from white patients in many aspects, such as younger-aged, more female patients, lower albumin level, higher quantitated IgG level, more anemia or hypertension, less lytic bone lesion,

more melphalan usage, more mobilization with growth factor, more thalidomide maintenance, less thalidomide usage, and less lenalidomide maintenance. We also showed that the hazard rate of progression or death among AA patients was significantly lower compared to that among white patients. Consistent with previous reports (Kroger et al., 2013), out study demonstrated that advanced stage and high-risk cytogenetics, the presences of bone lytic lesion, hypercalcemia, anemia and renal insufficiency were related to poor PFS and OS. However, unlike previous report that pre-transplant chemotherapy, mobilization and maintenance could improve OS or PFS (Liu & McCarthy, 2013), our study found that chemotherapy drugs thalidomide, DM, etoposide, cytoxytan and carboplatin, growth factor mobilization, thalidomide maintenance were related poor PFS and OS. Importantly, we found that the patients with response improvement by BMT had superior PFS.

One limitation is that this study is a single center study. All the collected patients were from Emory University Winship Cancer Institute. In this study, we found that some chemo-drug, maintenance and growth factor mobilization had the negative effect of some chemotherapy on treatment response, PFS and OS, which is inconsistent with previous study. The possible reason may come from the data collection process. We treat each drug usage as an independent variable without considering the drug combination. Actually, chemotherapy regimen and treatment process are more important. Often times, longer treatment or high-level drug usage mean poor response. If patients quickly get CR with common chemotherapy and short-term treatment and never got relapsed, they will not need high-level drug and long-term treatment. So, we detected some opposite effect in our study.

In conclusion, we showed that the radical disparity existed between AA and white MM patients. AA patients were younger-aged. AA have more female patients, lower albumin level, higher quantitated IgG level, more anemia or hypertension, less lytic bone lesion, more melphalan usage, more mobilization with growth factor, more thalidomide maintenance, less lenalidomide maintenance and more relapse after BMT. The hazard rate of progression or death among AA patients was significantly lower than white patients. We found that advanced stage, high-risk cytogenetics, high-cholesterol, renal insufficiency, presence of bone lytic lesion, hypercalcemia, and anemia were related with poor response, PFS or OS. The chemotherapy demonstrated opposite effect on treatment outcome. In the future, if we can improve our study design by stratifying patients with specific diagnosis stage or treatment group, the comparison and evaluation of treatment drugs or regimen would be more convincing.

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Appendix

Table 1: Univariate association of Race with covariates.

Covariate	Statistics*	level *	Race		p-value*
			AA n=370	White n=370	
age	Mean (SD)		54.91 (9.60)	58.88 (8.29)	0.0001
gender	N (%)	Male	172 (46.49%)	217 (58.56%)	
	N (%)	Female	198(53.51%)	153(41.35%)	0.0009
Stage_iss	N (%)	0	0(0)	1 (0.46%)	0.392
	N (%)	1	67 (28.76%)	74 (33.79%	
	N (%)	2	69 (29.61%)	65 (29.68%)	
	N (%)	3	97 (41.63%)	79 (36.07%)	
cytogenetics	N (%)	high	39 (18.06%)	44 (20.95%)	0.776
	N (%)	standard	24 (11.11%)	26 (12.38%)	
	N (%)	low / intermediate	61 (28.24%)	52 (24.76%)	
	N (%)	normal	92 (42.59%)	88 (41.9%)	
M spike value	Mean (SD)		12.4546 (111.6)	5.5694 (9.6480)	0.393
Plasma K/L	Mean (SD)		315.5 (5480.0)	328.6 (4442.0)	0.934
kappa	Mean (SD)		1134.0 (2409.8)	1216.7 (3349.5)	0.823
Lambda	Mean (SD)		1170.7 (3551.3)	586.2 (1661.4)	0.102
B2 microglobulin	Mean (SD)		5.5020 (6.5546)	5.3903 (6.5228)	0.865
Albumin	Mean (SD)		3.4007 (0.7939)	3.6583 (0.7100)	<0.001
Creatinine	Mean (SD)		2.3234 (4.1438)	3.3581 (19.6845)	0.432
Immunoglobulin	N (%)	IgG	232 (78.11%)	204 (71.83%)	0.129
	N (%)	IgM	1 (0.34%)	1 (0.35%)	
	N (%)	IgA	64 (21.55%)	77 (27.11%)	
	N (%)	IgD	0 (0%)	2 (0.7%)	
Quantiated Immunoglobulin	Mean (SD)	IgG	3393.8 (3100.2)	2627.7 (2634.8)	0.0146
	Mean (SD)	IgM	80.73 (603.7)	31.37 (41.8956)	0.2916
	Mean (SD)	IgA	1273.4 (2456.5)	1384.3 (3431.4)	0.749
plasmacytoma	N (%)	No	333 (90%)	318 (85.95%)	
	N (%)	Yes	37 (10%)	52 (14.05%)	
mugus	N (%)	No	333 (90%)	318 (85.95%)	0.09
	N (%)	Yes	37 (10%)	52 (14.05%)	
presence of lytic lesion	N (%)	No	175 (47.3%)	140 (37.84%)	0.009
	N (%)	Yes	195 (52.7%)	230 (62.16%)	
hypercalcemia	N (%)	No	140 (76.09%)	175 (77.09%)	0.811
	N (%)	Yes	44 (23.91%)	52 (22.91%)	
amyloidosis	N (%)	No	369 (99.73%)	370 (100%)	1
	N (%)	Yes	1 (0.27%)	0 (0%)	
anemia	N (%)	No	29 (11.37%)	83 (29.75%)	< 0.001
	N (%)	Yes	226 (88.63%)	196 (70.25%)	

			Race		
Covariate	**Statistics***	**level ***	**AA n=370**	**White n=370**	**p-value***
auto immu	N (%)	No	366 (98.92%)	363 (98.11%)	0.362
	N (%)	Yes	4 (1.08%)	7 (1.89%)	
B cell neoplasm	N (%)	No	369 (99.73%)	367 (99.19%)	0.624
	N (%)	Yes	1 (0.27%)	3 (0.81%)	
DM	N (%)	No	316 (85.41%)	331 (89.46%)	0.096
	N (%)	Yes	54 (14.59%)	39 (10.54%)	
DVT	N (%)	No	361 (97.57%)	363 (98.11%)	0.613
	N (%)	Yes	9 (2.43%)	7 (1.89%)	
High cholestrol	N (%)	No	316 (85.41%)	333 (90%)	0.057
	N (%)	Yes	54 (14.59%)	37 (10%)	
HTN	N (%)	No	198 (53.51%)	243 (65.68%)	<0.001
	N (%)	Yes	172 (46.49%)	127 (34.32%)	
other CA	N (%)	No	357 (96.49%)	347 (93.78%)	0.087
	N (%)	Yes	13 (3.51%)	23 (6.22%)	
Renal insufficiency	N (%)	No	129 (55.36%)	134 (50.95%)	0.326
	N (%)	Yes	104 (44.64%)	129 (49.05%)	
number of lines of	N (%)	0	2 (0.55%)	0 (0%)	0.5204
chemo	N (%)	1	263 (72.05%)	278 (75.34%)	
	N (%)	2	70 (19.18%)	60 (16.26%)	
	N (%)	3	20 (5.48%)	16 (4.34%)	
	N (%)	4	5 (1.37%)	9 (2.44%)	
	N (%)	5	3 (0.82%)	5 (1.36%)	
	N (%)	6	2 (0.55%)	1 (0.27%)	
Last chemo before	N (%)	RD	20 (5.41%)	30 (8.11%)	0.326
BMT	N (%)	RVD	139 (37.57%)	113 (30.54%)	
	N (%)	TD	25 (6.76%)	34 (9.19%)	
	N (%)	VD	38 (10.27%)	44 (11.89%)	
	N (%)	VDD	7 (1.89%)	8 (2.16%)	
	N (%)	VTD	56 (15.14%)	66 (17.84%)	
	N (%)	VTD-PACE	20 (5.41%)	19 (5.14%)	
	N (%)	other regimen	65 (17.57%)	56 (15.14%)	
Velcade	N (%)	No	64 (17.3%)	73 (19.73%)	0.394
	N (%)	Yes	306 (82.7%)	297 (80.27%)	
Revlimid	N (%)	No	173 (46.76%)	195 (52.7%)	0.106
	N (%)	Yes	197 (53.24%)	175 (47.3%)	
Thalidomide	N (%)	No	237 (64.05%)	209 (56.49%)	0.035
	N (%)	Yes	133 (35.95%)	161 (43.51%)	

Covariate	Statistics*	level *	Race		p-value*
			AA n=370	White n=370	
Dexamethasome/Prednisone	N (%)	No	21 (5.68%)	11 (2.97%)	0.071
	N (%)	Yes	349 (94.32%)	359 (97.03%)	
Melphalan	N (%)	No	299 (80.81%)	354 (95.68%)	<0.001
	N (%)	Yes	71 (19.19%)	16 (4.32)	
Vincristine	N (%)	No	367 (99.19%)	346 (93.51%)	1.000
	N (%)	Yes	3 (0.81%)	4 (1.08%)	
Doxorubicin / Doxil	N (%)	No	343 (92.7%)	346 (93.51%)	0.633
	N (%)	Yes	27 (7.3%)	24 (6.49%)	
Etoposide	N (%)	No	338 (91.35%)	338 (91.35%)	1.000
	N (%)	Yes	32 (8.65%)	32 (8.65%)	
Cytoxytan	N (%)	No	339 (91.62%)	351 (94.86%)	0.079
	N (%)	Yes	31 (8.38%)	19 (5.14%)	
Carboplatin	N (%)	No	340 (91.89%)	339 (98.38%)	0.894
	N (%)	Yes	30 (8.11%)	31 (838%)	
mobolization with Cytoxan	N (%)	No	297 (95.81%)	322 (94.71%)	0.511
	N (%)	Yes	13 (4.19%)	18 (5.29%)	
mobilization with growth factor	N (%)	No	60 (19.35%)	3 (0.88%)	< 0.001
	N (%)	Yes	250 (80.65%)	337 (99.12%)	
mobilization with mozobil	N (%)	No	299 (96.45%)	323 (95%)	0.363
	N (%)	Yes	11 (3.55%)	17 (5%)	
conditioning with Melphlan	N (%)	No	25 (7.62%)	28 (8.7%)	0.617
	N (%)	Yes	303 (92.38%)	294 (91.3%)	
Conditioning VTDPACE / DCEP/ cyclo / fludarabine	N (%)	No	304 (92.68%)	293 (9.99%)	0.431
	N (%)	Yes	24 (7.32%)	29 (9.01%)	
conditioning with Velcade	N (%)	No	348 (98.03%)	344 (97.45%)	0.605
	N (%)	Yes	7 (1.97%)	9 (2.55%)	
Maintenance after BMT	N (%)	No	100 (34.72%)	121 (41.58%)	0.089
	N (%)	Yes	188 (65.28%)	170 (58.42%)	
clinical trial or others	N (%)	No	314 (98.43%)	323 (97.88%)	0.601
	N (%)	Yes	5 (1.57%)	7 (2.12%)	
Lenalidomide	N (%)	No	159 (49.84%)	208 (63.03%)	< 0.001
	N (%)	Yes	160 (50.16%)	122 (36.97%)	
Thalidomide	N (%)	No	303 (94.98%)	297 (90%)	0.016
	N (%)	Yes	16 (5.02%)	33 (10%)	
Bortezomib	N (%)	No	266 (83.39%)	275 (83.33%)	0.986
	N (%)	Yes	53 (16.61%)	55 (16.67%)	
Toxicity	N (%)	No	48 (20%)	64 (24.43%)	0.234
	N (%)	Yes	192 (80%)	198 (75.57%)	

			Race		
Covariate	**Statistics***	**level ***	**AA n=370**	**White n=370**	**p-value***
infection	N (%)	No	240 (100%)	260 (99.24%)	0.500
	N (%)	Yes	0 (0%)	2 (0.76%)	
GI	N (%)	No	238 (99.17%)	258 (98.47%)	0.687
	N (%)	Yes	2 (0.83%)	4 (1.53%)	
neuropathy	N (%)	No	172 (71.67%)	185 (70.88%)	0.846
	N (%)	Yes	68 (28.33%)	76 (29.12%)	
Neutropenia	N (%)	No	238 (99.17%)	258 (98.47%)	0.687
	N (%)	Yes	2 (0.83%)	4 (1.53%)	
Rash	N (%)	No	237 (98.75%)	257 (98.09%)	0.726
	N (%)	Yes	3 (1.25%)	5 (1.91%)	
Thrombocytopenia	N (%)	No	239 (99.58%)	261 (99.62%)	1.000
	N (%)	Yes	1 (0.42%)	1 (0.38%)	

Table 2A: Univariate Logistic Regression of Race with Outcome: overall pretransplant response

			Overall Pretransplant Response (responded=1, not responded =0)		
Univariate	**level ***	**N**	**Odds Ratio (95% CI)**	**OR p-value**	**Type 3 p-value**
race	AA	258	1.452 (0.905, 2.329)	0.1218	0.1218
	White	264	-		

Table 2B: Univariate Logistic Regression of Race with Outcome: Day 100 overall response after BMT

			Day 100 aft BMT Overall Response (responded=1, not-responded =0)		
Univariate	**level ***	**N**	**Odds Ratio (95% CI)**	**OR p-value**	**Type 3 p-value**
race	AA	290	0.776 (0.424, 1.419)	0.4094	0.4094
	White	308	-		

Table 2C: Univariate Logistic Regression of Race with Outcome: Did BMT improve response

			Did BMT improve the response (yes=1, no =0)		
Univariate	**level ***	**N**	**Odds Ratio (95% CI)**	**OR p-value**	**Type 3 p-value**
race	AA	286	1.274 (0.828, 1.962)	0.2708	0.2708
	White	303	-		

Table 3A: Multivatiate Logistic Regression (backward selection)

		Overall Pretransplant Response		
Covariate	**level ***	**Odds Ratio (95% CI)**	**OR p-value**	**Logit p-value**
Race	AA	1.466 (0.871, 2.469)	0.1475	<0.0001
	White	-		
gender	Male	0.492 (0.289, 0.839)	0.0090	
	Female	-		
DM	Yes	0.432 (0.222, 0.842)	0.0135	
	No	-		
Cytoxytan	Yes	0.380 (0.150, 0.964)	0.0414	
	No	-		
Carboplatin	Yes	0.258 (0.105, 0.638)	0.0033	
	No	-		
Clinical trial drug	Yes	0.076 (0.012, 0.474)	0.0058	
	No	-		

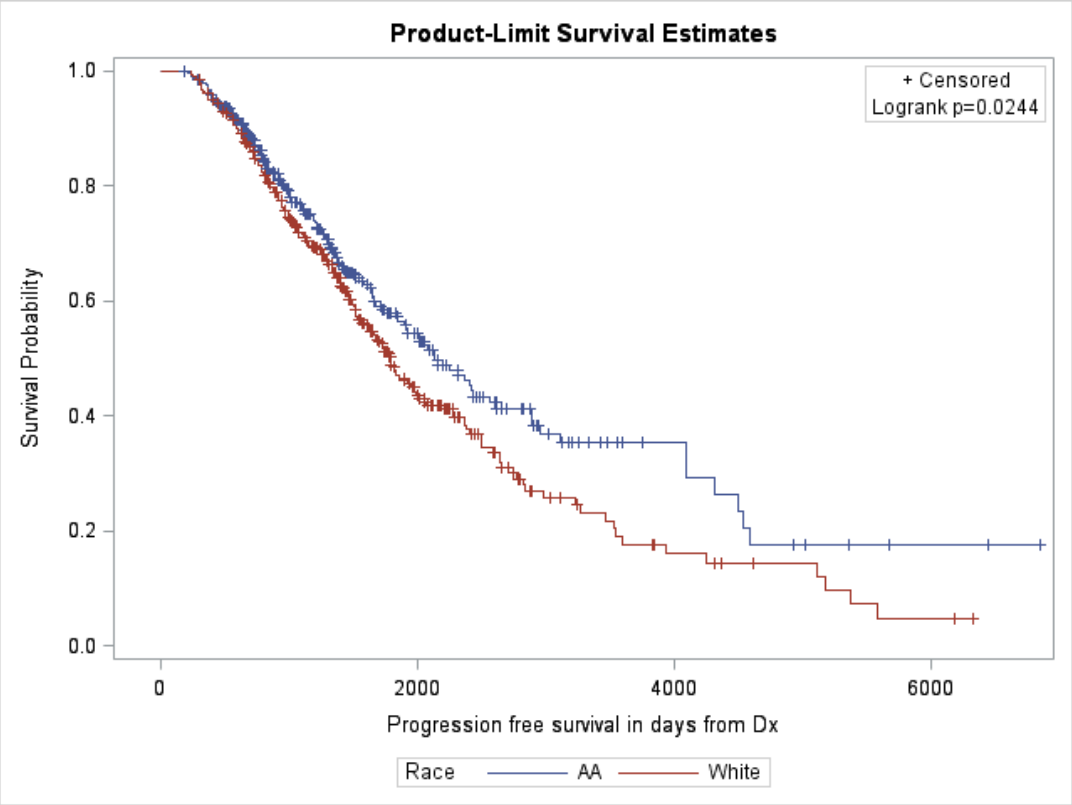
Table 3B: Multivatiate Logistic Regression (Stepwise selection)

		Day 100 aft BMT Overall Response		
Covariate	**level ***	**Odds Ratio (95% CI)**	**OR p-value**	**Logit p-value**
Race	AA	I (0, I)	0.9440	
	White	-		
Cytoxytan	Yes	0.050 (0.003, 0.866)	0.0395	
	No	-		

Table 3C: Multivatiate Logistic Regression (Stepwise selection)

		Did BMT improve the response (yes=1, no =0)		
Covariate	**level ***	**Odds Ratio (95% CI)**	**OR p-value**	**Logit p-value**
Race	AA	1.239 (0.710, 2.162)	0.4509	0.0116
	White	-		
Last chemo before BMT	RD	5.523 (1.153, 26.452)	0.0755	
	RVD	2.730 (1.028, 5.462)	0.3080	
	TD	1.572 (0.528, 4.683)	0.7641	
	VD / VDD	1.543 (0.616, 3.865)	0.6612	
	VTD	3.318 (1.207, 9.125)	0.0958	
	VTD-PACE	0.537 (0.181, 1.595)	0.0036	
	other regimen	-		

Figure 1 KM curves of race on PFS (Time from Diagnosis to Last Contact) in patients



Race	No. of Subject	Event	Censored	Median Survival (95% CI)
AA	365	143 (39.18%)	222 (60.82%)	2130 (1847, 2559)
White	370	207 (55.95%)	163 (44.05%)	1795 (1613, 1979)

Table 4A: Univatiate Progression Free Survival Analysis amongst all patients

			Progression free survival in days from Dx			
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Assumption P-value**	**Log-rank P-value**
Race	AA	325	0.783 (0.632-0.969)	0.0248	0.0248	**0.0244**
	White	290	-	-		
Stage	0	1	0 (0 – I)	0.9708	0.0035	**0.0021**
	1	140	0.532 (0.380 – 0.744)	0.0002		
	2	133	0.798 (0.576 - 1.107)	0.1765		
	3	174	-	-		
Cytogenetics	High	82	1.439 (0.956 – 2.165)	0.0808	0.0469	**0.0438**
	Standard	50	1.841 (1.170 – 2.897)	0.0084		
	Low/Intermediate	112	1.260 (0.853 - 1.860)	0.2459		
	Normal	179	-	-		
Presence of lytic lesion	Yes	422	1.346 (1.084 - 1.672)	0.0071	0.0071	**0.0069**
	No	313	-			
Hypercalcemia	Yes	95	2.104 (1.558 - 2.840)	< 0.0001	<0.0001	**<0.0001**
	No	314	-			
Anemia	Yes	410	1.725 (1.238 - 2.404)	0.0013	0.0013	**0.0011**
	No	111	-			
Renal Insufficiency	Yes	232	1.330 (1.030-1.717)	0.0287	0.0287	**0.0281**
	No	262	-	-		
Last treatment regimen	RD	50	1.435 (0.920 - 2.236)	0.1110	<0.0001	**<0.0001**
	RVD	250	1.002 (0.707 - 1.422)	0.9898		
	TD	59	1.392 (0.942 - 2.056)	0.0966		
	VD/VDD	97	1.407 (0.966 - 2.050)	0.0752		
	VTD	121	1.541 (1.083 - 2.193)	0.0163		
	VTD-PACE	39	3.209 (2.072 - 4.970)	<0.0001		
	Other regimen	119	-			
Number of lines prior to transplantation	0	2	0.000 (0.000 - I)	0.9751	0.0207	**0.0099**
	1	539	2.609 (0.641- 10.625)	0.1808		
	2	129	4.059 (0.985 - 16.722)	0.0525		
	3	34	3.158 (0.735 - 13.570)	0.1222		

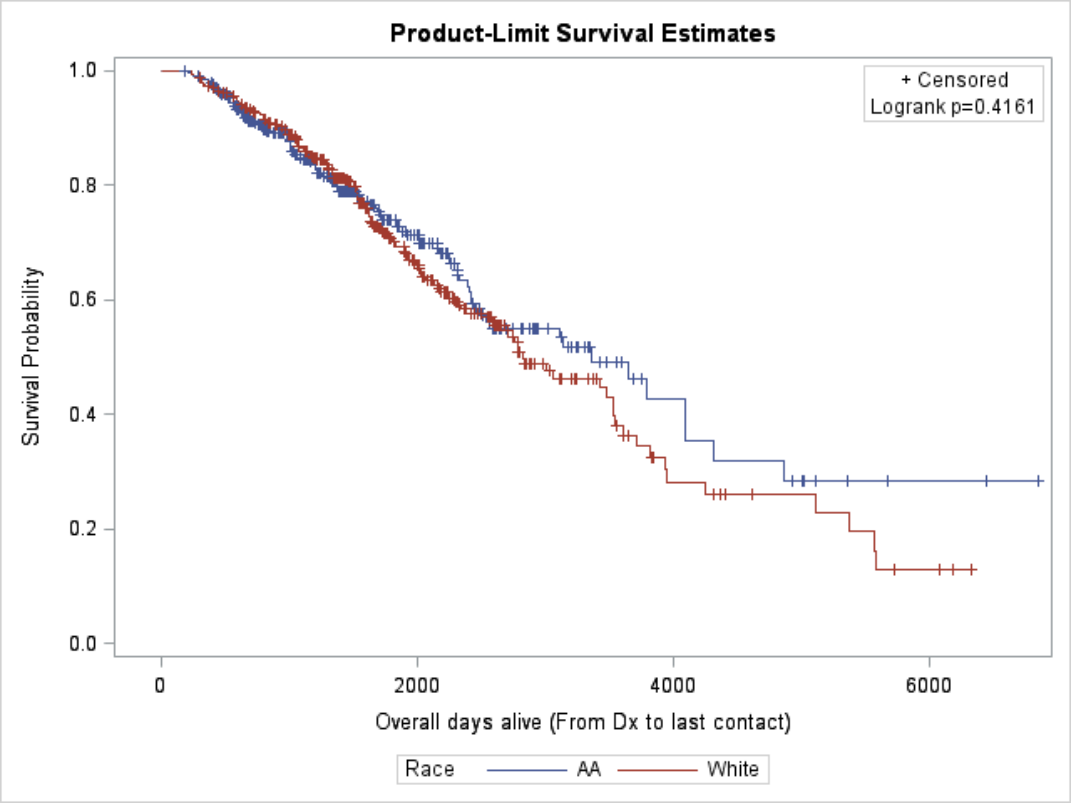
Table 4A: Univatiate Progression Free Survival Analysis amongst all patients

			Progression free survival in days from Dx			
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Assumption P-value**	**Log-rank P-value**
	4	14	2.890 (0.630 - 13.258)	0.1721		
	5	8	2.019 (0.405 - 10.078)	0.3916		
	6	3	-			
Thalidomide	Yes	292	1.450 (1.174 - 1.792)	0.0006	0.0006	**0.0005**
	No	443	-			
Dexamethasone	Yes	704	2.656 (1.445 - 4.882)	0.0017	0.0017	**0.0011**
	No	31	-			
Etoposide	Yes	64	1.811 (1.331 - 2.465)	0.0002	0.0002	**0.0001**
	No	671				
Cytoxytan	Yes	50	1.560 (1.088 - 2.238)	0.0156	0.0156	**0.0147**
	No	685				
Carboplatin	Yes	61	1.950 (1.427-2.665)	<0.0001	<0.0001	**<0.0001**
	No	674	-	-		
Mobilization with growth factor	Yes	585	2.107 (1.084 - 4.096)	0.0280	0.0280	**0.0246**
	No	63	-			
Maintenane with Thalidomide	Yes	49	1.430 (1.011 - 2.022)	0.0433	0.0433	**0.0422**
	No	598	-			
Did transplant improve response	Yes	509	0.773 (0.574 – 1.042)	0.0910	0.0910	**0.0904**
	No	173	-			
Immunoglobulin at day 100	IgG	280	1.370 (0.965 - 1.945)	0.0781	0.0254	**0.0142**
	IgM	5	1.692 (0.603 – 4.753)	0.3181		
	IgA	63	1.822 (1.184 - 2.805)	0.0064		
	IgD	1	9.060 (1.224 - 67.086)	0.0310		
	Normal	97	-			
lambda	242		1.000 (1.000 – 1.000)	0.0016	0.0016	**0.0102**
β2-microglobulin	401		1.039 (1.021 - 1.057)	<0.0001	<0.0001	**<0.0001**
Albumin	394		0.707 (0.576 - 0.868)	0.0009	0.0009	**0.0010**
Quantiated IgA	293		1.000 (1.000 - 1.000)	0.0308	0.0308	**0.0331**
Kappa at day 100	533		1.001 (1.0001 – 1.002)	<0.0001	<0.0001	**<0.0001**
Plasma k/l at day 100	507		1.001 (1.000 – 1.001)	0.0021	0.0021	**<0.0001**

Table 4B: Multivariate Overall Survival Analysis amongst all patients (Backward selestion)

Covariate	level *	Hazard Raio (95% CI)	HR p-value	Assumption p-value	Log-rank p-value
Race	AA	0.836 (0.377, 1.854)	0.6588	0.6588	0.0165
	White	-			
Thalidomide	Yes	2.764 (1.339 – 5.707)	0.0060	0.0060	
	No	-			

Figure 2 KM curves of race on overall survival (Time from Diagnosis to Last Contact) in patients



Race	No. of Subject	Event	Censored	Median Survival (95% CI)
AA	365	100 (27.40%)	265 (72.60%)	3361.00 (2494.00, 4098.00)
White	370	143 (38.65%)	227 (61.35%)	2820.00 (2592.00, 3538.00)

Table 5A:Univariate Associate of Race with Overall Survival Analysis amongst all patients

Covariate	level *	N	Hazard Raio (95% CI)	HR p-value	Assumption p-value	Log-rank p-value
Race	AA	325	0.899 (0.696 - 1.162)	0.4163	0.4163	0.415
	White	290	-	-		
Stage_iss	0	1	0.000 (0.000, NA)	0.9807	<0.0001	<0.0001
	1	140	0.364 (0.240, 0.554)	<0.0001		
	2	133	0.486 (0.319, 0.742)	0.0008		
	3	174	-			
cytogenetics	high	82	2.372 (1.439 - 3.910)	0.0007	0.0013	0.0013
	standard	50	2.178 (1.330 - 3.885)	0.0084		
	low / intermediate	112	2.140 (1.327 - 3.451)	0.0018		
	normal	179	-			
presence of lytic lesion	Yes	422	1.347 (1.038 - 1.748)	0.0252	0.0252	0.0237
	No	313	-			
Hyper-calcemia	Yes	95	2.429 (1.708 - 3.454)	<0.0001	<0.0001	<0.0001
	No	314	-			
anemia	Yes	420	1.948 (1.274 - 2.979)	0.0021	0.0021	0.0009
	No	111	-			
DM	Yes	93	1.533 (1.069 - 2.198)	0.0201	0.0201	0.027
	No	642	-			
Renal insufficiency	Yes	232	1.390 (1.017 - 1.899)	0.0391	0.0391	0.0393
	No	262	-			
number of lines of chemo	0	2	0.000 (0.000, I)	0.9732	0.025	0.0108
	1	539	3.467 (0.480, 25.024)	0.2176		
	2	129	5.362 (0.736, 39.084)	0.0975		
	3	34	5.717 (0.756, 43.213)	0.0911		
	4	14	6.487 (0.827, 50.902)	0.0753		
	5	8	3.996 (0.479, 33.339)	0.2006		
	6	3	-			
Last chemo before BMT	RD	50	1.015 (0.591 - 1,741)	0.9572	<0.0001	<0.0001
	RVD	250	0.841 (0.533 - 1.279)	0.4184		
	TD	24	0.737 (0.453 - 1.198)	0.218		
	VD / VDD	34	1.100 (0.711, 1.701)	0.67		
	VTD	43	1.114 (0.735 - 1.689)	0.61		
	VTD-PACE	28	3.389 (2.130, 5.392)	<0.0001		
	other regimen	54	-			
Velcade	Yes	598	1.370 (1.009 - 1.861)	0.0439	0.0439	0.0384
	No	137	-			
Thalidomide	Yes	292	1.291 (1.000 - 1.668)	0.0504	0.0504	0.0498
	No	443	-			
Dexamethaso	Yes	704	2.459 (1.199 - 5.042)	0.014	0.014	0.0049

me/Prednisone	No	31	-			
Doxorubicin / Doxil	Yes	51	1.456 (0.968 - 2.191)	0.0716	0.0716	0.086
	No	684	-			
Cytoxytan	Yes	50	2.227 (1.517 - 3.269)	<0.0001	<0.0001	0.0002
	No	685	-		-	
Carboplatin	Yes	61	2.484 (1.760 - 3.506)	<0.0001	<0.0001	<0.0001
	No	674	-			
Etoposide	Yes	64	2.307 (1.644 - 3.238)	<0.0001	<0.0001	<0.0001
	No	671	-			
mobilization with growth factor	Yes	585	1.964 (0.870 - 4.437)	0.1044	0.1044	0.0979
	No	63	-			
Immunoglobulin at day 100 after BMT	IgG	280	1.219 (0.797 - 1.863)	0.3612	0.0744	0.0544
	IgM	5	2.092 (0.731 - 5.989)	0.1689		
	IgA	63	1.936 (1.176 - 3.185)	0.0093		
	IgD	1	0.000 (0.000, NA)	0.9833		
	Normal	97	-			
Maintenance with Bortezomib	Yes	108	2.038 (1.423 - 2.919)	0.0001	0.0001	<0.0001
	No	539	-			

Table 5B: Multivariate Overall Survival Analysis amongst all patients (Backward selestion)

Covariate	level *	Hazard Raio (95% CI)	HR p-value	Assumption p-value	Log-rank p-value
Race	AA	1.541 (0.708, 3.353)	0.2755	0.2755	0.0041
	White	-			
Stage_iss	1	0.674 (0.291 - 1.564)	0.3584	0.0423	
	2	0.285 (0.107 - 0.750)	0.0121		
	3	-			
Hyperclcemia	Yes	2.349 (0.978 - 5.644)	0.0561	0.0208	
	No	-			
Cytogenetics	0	2.797 (1.078, 7.255)	0.0344	0.0561	
	1	0.960 (0.287, 3.206)	0.9469		
	2	3.071 (1.348, 7.000)	0.0076		
	3	-			