Beta-blockers improve survival outcomes in patients with multiple myeloma: a retrospective evaluation

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A preclinical study demonstrated anti-proliferative and apoptotic effect of propranolol on multiple myeloma (MM) cell. Clinical studies suggested that beta-blocker (BB) might impact the prognosis of breast, prostate, colorectal, ovarian, lung, and skin cancer. This retrospective study evaluated the effect of BB in MM disease-specific survival (DSS) and overall survival (OS). Among 1,971 newly diagnosed MM patients seen at Mayo Clinic between 1995 and 2010, usage of BB and other cardiac (or antihypertensive) medications were abstracted. Cumulative incidence function and Kaplan–Meier method were used to estimate 5-year cumulative incidence rate (CIR) of MM death and OS rate, respectively. Nine hundred and thirty (47.2%) patients had no intake of cardiac medications; 260 (13.2%) used BB alone; 343 (17.4%) used both BB/non-BB cardiac medications; and 438 (22.2%) had non-BB cardiac drugs. Superior MM DSS was observed in BB only users, compared to patients without any cardiac drugs (HRCSadj: 0.53, 95% confidence interval [CI], 0.42–0.67, Padj < 0.0001) and non-BB cardiac drugs users (HRCSadj: 0.49, 95% CI, 0.38–0.63, Padj < 0.0001). Patients on both BB and other cardiac drugs showed superior DSS than non-cardiac drugs users (HRCSadj: 0.54, 95% CI, 0.44–0.67, Padj < 0.0001) and non-BB cardiac drug users. (HRCSadj: 0.50, 95% CI, 0.40–0.62, Padj < 0.0001). MM DSS did not differ between BB users with and without other cardiac drugs (Padj = 0.90). Multivariable analysis showed the same pattern for OS. In patients with MM, BB intake is associated with a reduced risk of disease-specific death and overall mortality in comparison to non-BB or no use of cardiac drugs.

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Introduction

Preclinical studies have demonstrated that beta-blocker (BB) could inhibit multiple cellular activities such as cell proliferation, invasion, migration, angiogenesis, and tumor immune response that are involved in cancer progression and metastasis by interfering with the β-adrenergic receptor signaling pathway [1]. Recently a number of clinical observational studies tested the hypothesis that BB treatment might impact the prognosis of breast, prostate, colorectal, ovarian, lung, and skin cancer [2–11]. However the findings were inconsistent [1] and the possible impact of BB on cancer outcomes remains controversial. In vitro, the non-selective BB, propranolol, has anti-proliferative and apoptotic activity on a multiple myeloma (MM) cell line [12]. In the absence of outcome data related to BB use in MM, we conducted this study to investigate the association between BB use and survival outcomes in MM patients.

Methods

Patients. This study was approved by the Mayo Clinic Institutional Review Board. Only patients who had provided prior consent for research directed access to their medical records were included. We excluded patients with coexisting amyloidosis, those without information related to the use of cardiac (or antihypertensive) drugs or MM therapies, and those without follow up or survival information in the medical records. Data extracted from the Mayo Clinic electronic medical records included date of birth, gender, date of diagnosis, initial diagnostic data of radiologic, histopathological and laboratory tests, performance status (PS), International Staging System (ISS), cardiac history and medications including BB usage documented for a minimum of 3 months at any time after diagnosis of MM (if any), cytogenetic and fluorescent in situ hybridization (FISH) risk strata based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) [13], stem cell transplant, MM therapies, date of death or last follow up and cause of death. Of 2104 newly diagnosed MM patients seen at Mayo Clinic, Rochester between 1995 and 2010 within 90 days of diagnosis, 1,971 patients met all inclusion criteria. These patients were categorized into four groups based on their cardiac or antihypertensive medication intake history: patients without any cardiac (or antihypertensive) medications; patients taking BB alone (e.g., metoprolol, atenolol, carvedilol, propranolol); those who only took non-BB cardiac (or antihypertensive) drugs (e.g., ACE inhibitor, calcium channel blocker, angiotensin II receptor blocker, diuretic); and patients on BB and other non-BB cardiac medications.

Additional Supporting Information may be found in the online version of this article.

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The MM disease-specific survival (DSS) and overall survival (OS) were the primary endpoints. OS was defined as the time from the date of diagnosis to the date of death due to all causes, and living patients were censored at the last follow-up date. The causes of death were identified and categorized as due to MM, cardiac disease, and other reasons. DSS was defined as the time from diagnosis to death caused by MM. Cardiac and other deaths were the competing events for MM cause-specific deaths. The demographics, disease characteristics of patients, and chemotherapies administered were summarized by median (range) and frequency (percentage) for continuous and categorical factors, respectively, per BB intake groups. These patient characteristics were compared among the BB usage groups using Kruskal Wallis test or Chi-Squared test as appropriate. Cumulative incidence functions and Kaplan–Meier method were used to estimate the 5-year cumulative incidence rate (CIR) of MM death and OS rate, respectively. In univariate analysis, OS were compared among BB intake groups by log-rank test. To account for the competing risks, DSS were compared among groups by Gray’s test. Adjusted cause-specific hazard ratio (HR_CCS) and hazard ratio (HR_adj) was

| TABLE I. Characteristics Comparison Among Cardiac Medication Usage Groups |
|---------------------------------------------------------------|
| No cardiac medications (N = 930) | Beta-blocker and other cardiac medications (N = 343) | Non-beta-blocker cardiac medications (N = 438) | Total (N = 1971) | P value |
| Age at diagnosis | | | | <0.0001* |
| N | 930 | 260 | 438 | 1971 |
| Median | 60.0 | 64.0 | 68.0 |
| Range (22.0–91.0) | (37.0–92.0) | (32.0–94.0) | (29.0–92.0) | (22.0–94.0) |
| Gender | | | 0.3164** |
| Female | 394 (42.4%) | 98 (37.7%) | 129 (37.6%) | 173 (39.5%) | 794 (40.3%) |
| Male | 536 (57.6%) | 162 (62.3%) | 214 (62.4%) | 265 (60.5%) | 1177 (59.7%) |
| mSMART | | | 0.4016** |
| Standard Risk | 271 (62.9%) | 107 (58.8%) | 166 (56.3%) | 171 (60.9%) | 611 (60.4%) |
| Intermediate Risk | 110 (25.5%) | 45 (24.7%) | 54 (26.2%) | 44 (22.9%) | 253 (25.0%) |
| High Risk | 50 (11.6%) | 30 (16.5%) | 36 (17.5%) | 31 (16.1%) | 147 (14.5%) |
| Missing | 499 | 78 | 137 |
| International Staging System | | | <0.0001** |
| I | 330 (37.9%) | 92 (36.7%) | 90 (27.2%) | 117 (28.2%) | 629 (33.7%) |
| II | 385 (44.2%) | 96 (38.2%) | 119 (36.0%) | 172 (41.4%) | 772 (41.3%) |
| III | 156 (17.9%) | 63 (25.1%) | 122 (36.9%) | 126 (30.4%) | 467 (25.0%) |
| Missing | 59 | 9 | 12 |
| Performance Score | | | 0.1287** |
| 0 | 360 (41.6%) | 108 (43.5%) | 126 (39.1%) | 167 (41.6%) | 761 (41.4%) |
| 1 | 332 (38.4%) | 91 (39.1%) | 107 (33.2%) | 140 (34.9%) | 670 (36.5%) |
| 2+ | 173 (20.0%) | 49 (19.8%) | 89 (27.6%) | 94 (23.4%) | 405 (22.1%) |
| Missing | 65 | 12 | 21 | 37 | 135 |
| Diagnosis Year | | | <0.0001** |
| 1995–1999 | 240 (25.8%) | 37 (14.2%) | 107 (33.2%) | 91 (20.8%) | 407 (20.6%) |
| 2000–2004 | 291 (31.3%) | 77 (29.6%) | 119 (36.0%) | 172 (41.4%) | 620 (31.5%) |
| 2005–2010 | 399 (42.9%) | 146 (56.2%) | 196 (57.1%) | 203 (46.3%) | 944 (47.9%) |
| Pomalidomide | | | 0.0144** |
| No | 861 (92.6%) | 229 (88.1%) | 311 (90.7%) | 414 (94.5%) | 1815 (92.1%) |
| Yes | 69 (7.4%) | 31 (11.9%) | 32 (9.3%) | 24 (5.5%) | 156 (7.9%) |
| Lenalidomide | | | 0.0250** |
| No | 578 (62.2%) | 147 (51.8%) | 205 (59.8%) | 295 (67.4%) | 1225 (62.2%) |
| Yes | 352 (37.8%) | 113 (41.8%) | 138 (40.2%) | 143 (32.6%) | 746 (37.8%) |
| Thalidomide | | | 0.2777** |
| No | 666 (71.8%) | 189 (72.7%) | 262 (76.4%) | 331 (75.6%) | 1450 (73.6%) |
| Yes | 262 (28.2%) | 71 (27.3%) | 81 (23.6%) | 107 (24.4%) | 521 (26.4%) |
| Stem cell transplant | | | <0.0001** |
| No | 480 (51.6%) | 116 (44.6%) | 204 (59.5%) | 288 (65.6%) | 1088 (55.2%) |
| Yes | 450 (48.4%) | 144 (55.4%) | 139 (40.5%) | 150 (34.2%) | 883 (44.8%) |
| Alkylator | | | 0.2767** |
| No | 457 (50.7%) | 114 (44.4%) | 167 (49.7%) | 216 (51.6%) | 954 (49.9%) |
| Yes | 444 (49.3%) | 143 (55.6%) | 169 (50.3%) | 203 (48.4%) | 959 (50.1%) |
| Missing | 29 | 3 | 7 | 19 | 58 |
| Anthracycline | | | <0.0001** |
| No | 694 (77.0%) | 251 (83.7%) | 295 (87.8%) | 371 (88.5%) | 1575 (82.3%) |
| Yes | 207 (23.0%) | 42 (16.3%) | 41 (12.2%) | 48 (11.5%) | 338 (17.7%) |
| Missing | 29 | 3 | 7 | 19 | 58 |
| Bortezomib | | | 0.0010** |
| No | 677 (75.1%) | 167 (65.0%) | 257 (76.5%) | 328 (78.3%) | 1429 (74.7%) |
| Yes | 224 (24.9%) | 90 (35.0%) | 79 (23.5%) | 91 (21.7%) | 484 (25.3%) |
| Missing | 29 | 3 | 7 | 19 | 58 |
| Carfilzomib | | | 0.4177** |
| No | 882 (97.9%) | 251 (97.7%) | 328 (97.6%) | 415 (99.0%) | 1876 (98.1%) |
| Yes | 19 (2.1%) | 6 (2.3%) | 8 (2.4%) | 4 (1.0%) | 37 (1.9%) |
| Missing | 29 | 3 | 7 | 19 | 58 |
| Ixazomib | | | 0.0368** |
| No | 887 (98.4%) | 246 (95.7%) | 328 (97.6%) | 413 (98.6%) | 1874 (98.0%) |
| Yes | 14 (1.6%) | 11 (4.3%) | 8 (2.4%) | 6 (1.4%) | 39 (2.0%) |
| Missing | 29 | 3 | 7 | 19 | 58 |

* Kruskal Wallis
b Chi-Squared.
estimated using Cox proportional hazard model for OS and DSS, respectively, adjusting for demographics, disease characteristics, diagnosis year, and various chemotherapies. Interaction test was performed to explore whether MM therapies influenced the association between BB usage and outcomes. All statistical analyses were carried out in SAS 9.4 software (SAS Institute, Cary, NC). Statistical significance was inferred at $P\text{-value} < 0.05$ for all comparisons.

**Results**

Among this group of 1,971 patients, 930 (47.2%) had no cardiac medication intake (either no cardiovascular history or borderline hypertension without treatment requirements); 260 (13.2%) used a BB for a minimum of 3 months any time after diagnosis of MM; 343 (17.4%) had intake of both BB ($\geq 3$ months) and non-BB cardiac medications; and 438 patients (22.2%) only took other categories of non-BB cardiac drugs. The indications for cardiac medications included hypertension, coronary artery disease, congested heart failure, cardiac dysrhythmia, valvular heart disease, pulmonary hypertension, angina, and myocardial infarct. These four groups of BB users and nonusers were compared with regard to clinical characteristics as age, gender, year of diagnosis, ISS stage, PS, mSMART classification, and MM therapies (Table I). There were no statistically significant differences in age, PS and mSMART classification between the four groups. However, the patients who did not take cardiac medications were younger compared to those who took BB, BB plus non-BB cardiac medications, and other non-BB cardiac medications (median age 60, 64, 68 and 68 years old, respectively; $P < 0.0001$), were less likely to present with ISS stage 3 disease ($17.9\%$ vs. $25.1\%$, $36.9\%$, and $30.4\%$ respectively; $P < 0.0001$), and more likely to be diagnosed before year of 2000 (25.8% vs. 14.2%, 11.4%, 20.8% respectively; $P < 0.0001$). Patients in the BB only group had higher use of bortezomib ($P = 0.001$), lenalidomide ($P = 0.025$), pomalidomide ($P = 0.0144$), ixazomib ($P = 0.0368$), and autologous stem cell transplant (ASCT) ($P < 0.0001$).

At the time of this analysis, 1,345 patients were died. The estimated median follow up for those alive was 74.3 months. Figure 1 shows the cumulative Incidence curves for MM-specific death. Significant differences in cumulative incidence rates (CIR) of MM-specific death overtime were shown among four BB intake groups by Gray’s test, accounting for competing risks of cardiac and other deaths. Patients who took only BB had the lowest 5-year CIR of MM-specific death 23.5% ($95\%$ confidence interval (CI), 18.8–29.4%), followed by those taking both BB and other cardiac drugs (31.9%, 95%CI, 27.2–37.4%) and those without any documentation of cardiac (or antihypertensive) drugs use (41.3, 95% CI, 38.2–44.7%). The patients who took non-BB cardiac medications had the highest 5-year CIR of MM-specific death (49.9%, 95% CI, 45.3–54.9%). Figure 2 shows the Kaplan–Meier estimates of OS. Log-rank test shows significant difference in OS among four BB intake groups ($P < 0.0001$). The patients who took only BB had highest 5-year OS rate at 66.0% (95% CI, 60.5–72.1%) and the patients who took non-BB cardiac medications had lowest 5-year OS rate at 39.3% (95% CI, 34.9–44.2%). The patients who took BB plus other cardiac drugs and who had no cardiac drugs had similar 5-year OS rate, 49.6% and 50.0%, respectively (Supplementary Information Table I).

Cytogenetic and FISH stratification is an important prognostic factor, but the data were unavailable in some patients especially for
those who were diagnosed in early years. We first performed a multivariable (MV) analysis to adjust for age, gender, year of diagnosis, performance score, and MM therapies for all patients. An additional analysis with a smaller subset of patients who had cytogenetic/FISH performed (n = 915) was also done. Despite the reduced sample size, the MV analyses results were consistent irrespective of the high-risk FISH, that is, deletion 17p, t(14;16), or t(14;20). Therefore, we only presented the adjusted association estimates based on the MV model without FISH risk in Table II. Both superior MM DSS and OS were observed for patients taking BB only compared to those taking non-BB cardiac drugs (DSS: HR\text{CS adj.}, 0.49, 95% CI, 0.38–0.63, P\text{adj.} < 0.0001; OS: HR\text{adj.}, 0.62, 95% CI, 0.50–0.76, P\text{adj.} < 0.0001), and compared to those with no record of cardiac drugs (DSS: HR\text{CS adj.}, 0.53, 95% CI, 0.42–0.67, P\text{adj.} < 0.0001; OS: HR\text{adj.}, 0.67, 95% CI, 0.55–0.81, P\text{adj.} < 0.0001). The patients who received both BB and other cardiac drugs also had superior MM DSS than those who did not use cardiac drugs (HR\text{CS adj.}, 0.54, 95% CI, 0.44–0.67, P\text{adj.} < 0.0001) and those who used non-BB cardiac drugs (HR\text{CS adj.}, 0.50, 95% CI, 0.40–0.62, P\text{adj.} < 0.0001). The same pattern was observed for OS. There are no difference in MM DSS (P\text{adj.} = 0.90) and OS (P\text{adj.} = 0.36) between BB users who took other cardiac drugs or not.

Of note, in multivariable analysis adjusting for prognostic factors, the improved survival outcome from BB was independent of MM therapies. We further evaluated whether various chemotherapies impacted the observed association between BB usage and survival. The interaction tests between four cardiac medication usage groups and each MM treatment agent was not significant in either univariate or multivariate analyses (Supplementary Information Table II). The improved survival benefit of BB was independent and additional to the effect of MM therapies.

**Discussion**

This study was designed to evaluate the prognostic association of BB usage with survival among patients with MM. We found that the use of BB was associated with longer OS and DSS in MM patients even after adjustment for prognostic factors, suggesting that BB usage was independently associated with better MM prognosis. Our findings are concordant with the emerging evidence suggesting that BB reduce cancer progression and metastasis [1]. Preclinical studies have suggested that the β-adrenergic signaling pathway regulates multiple developmental process in cell proliferation, differentiation and migration [1]. Epinephrine and norepinephrine are released during stress response, and activate β-adrenergic receptors (β-ARs) [1]. Activation of β-adrenergic signaling results in promotion of inflammation by induction of pro-inflammatory cytokine interleukin 6 (IL-6), overexpression of vascular endothelial growth factor (VEGF) leading to angiogenesis—a critical process for tumor growth and progression [1], enhancing tumor cells to invade the extracellular matrix [14], and decreased sensitivity to apoptosis of cancer cells [15]. Because BB blocks the action of catecholamine on β-ARs, these agents have been explored, both in vitro and in vivo, and found to have antitumor effect in ovarian, breast, colon, prostate, pancreatic and small cell lung cancer [16–21]. In MM, bone marrow angiogenesis is stimulated by the malignant plasma cells in the bone marrow microenvironment [22]. Bone marrow angiogenesis, driven by several angiogenic factors including VEGF and IL-6 [23], has been associated with disease.

![Figure 2](image_url)

**Figure 2.** The patients who took only BB had highest 5-year OS rate at 66.0%, and non-BB cardiac medications users had lowest 5-year OS rate at 39.3%. The patients who took BB plus other cardiac drugs and who had no cardiac drugs had similar 5-year OS rate, 49.6% and 50.0%, respectively.
aggressiveness of myeloma and disease progression from monoclonal gammopathy of undetermined significance (MGUS) to MM [24]. In vitro studies have shown that production and up regulation of VEGF and IL-6 are inhibited by BB [25,26]. A recent in vitro experiment also suggested that BB affects NF-kB signaling in MM cells by regulating the expression levels of genes involved in upstream and downstream pathways [12]. BB caused an increase of antiapoptotic Bcl-2 protein, which is a main target of MM treatment [12], and is one of the major pathways mediating the expression levels of genes involved in upstream and downstream pathways [12]. BB caused an increase of apoptotic Bcl-10 protein which is an important transducer of apoptosis [12].

Our observation adds to the growing evidence of improved survival among oncology patients receiving BB including non-small cell lung cancer [2], ovarian cancer [3,4] and colorectal cancer [5]; prostate (reduced cancer specific mortality) [6,7] and breast cancer [8,9]; and melanoma [10,11]. Other positive studies have shown increased response to chemotherapy in patients with neuroblastoma [28], better response to radiation therapy in meningioma [29], and decreased risk of progression in melanoma [10,11]. The evidence is conflicting since the NF-kB signaling pathway is a main target of MM treatment [12], and is one of the major pathways by which proteasome inhibitors effect MM cell death [27]. It is through these pathways that BB may impact MM survival.

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