Cardiovascular Complications of Modern Multiple Myeloma Therapy: A Pharmacovigilance Study

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Abstract

Background: Multiple myeloma accounts for over 15% of hematological malignancies. In attempt to tackle this malady, the FDA approved four drugs in 2015 which has propagated further development of new anti-multiple myeloma since. However, the health safety of these new agents is still ill-defined. The aim of this study is to delineate the cardiovascular adverse events of these drugs. Methods: We searched the cardiac adverse events of the newly approved FDA drugs since 2015 using the U.S. Food and Drug Administration Adverse Events Reporting System database (FAERS). We calculated the reporting odds ratio (ROR) with 95% confidence for four drugs that have the highest incidence of cardiovascular adverse events. Results: Among the medications that have approved for MM Between 2015-2020, four novel drugs showed the highest incidence of cardiotoxicity. ROR (95% CI) for atrial fibrillation due to elotuzumab, Ixazomib, daratumumab, and panobinostat compared to other FAERS drugs was 5.8 (4.4-7.7), 1.9 (1.5-2.3), 4.8 (4.2-5.6), and 5.7 (4.1-8.1), respectively. The ROR (95% CI) for cardiac failure was 8.2 (6.4-10.5), 4.7 (4.1-5.4), 5.8 (4.9-6.7), and 5.6 (3.8-8.1) and ROR (95% CI) for coronary disease was 2.7 (1.9-3.9), 2.7 (2.3-3.2), 2.3 (1.9-2.8), and 4.6 (3.2-6.6) due to elotuzumab, Ixazomib, daratumumab, and panobinostat versus all other drugs in FAERS. Conclusions: Our results demonstrated that the newly approved antimyeloma therapy (elotuzumab, Ixazomib, daratumumab, panobinostat) are significantly associated previously unknow cardiotoxicity. These results warrant further studies and highlight the importance of considering the cardiac history of patients with multiple myeloma when utilizing these novel agents.

Introduction:

Multiple myeloma is characterized by neoplastic proliferation of plasma cells that produce monoclonal immunoglobulins. Proliferation of cells in the bone marrow often causes osteolytic lesions, osteopenia and/or pathologic fractures, subsequent hypercalcemia stemming from bone destruction and anemia mainly due to bone marrow replacement[1]. There is also observed renal dysfunction due to accumulation and precipitation of light chains which form casts in distal renal tubules [2]. It is estimated that 35000 new cases are diagnosed annually, accounting for nearly 2% of all new cancer diagnoses[3]. Age-adjusted death rates have not changed significantly over 2009–2018 and have remained at around 3.1 per 100,000 population[3].

While the initial therapy before newer therapeutic advances has classically consisted of VRd (bortezomib + lenalinomide + dexamethasone) and/or stem cell transplant with bortezomib/lenalinomide maintenance[4], we have had newer approvals for treatment of multiple myeloma which have received at least one previous regimen. Between 2015-2016, the FDA approved 4 new drugs – elotuzumab (activates NK cells)[5], ixazomib (proteosome inhibitor)[6], daratumumab (targeting CD38)[7], panobinostat(histone deacetylase inhibitor)[8] and more recently belantamab and selinexor in 2020[9,10]. Clinical Daratumumab is frequently used in first line regimens along with VRd as D-VRd[4].

While the usage of these drugs has increased in the recent years, there is little published evidence about their cardiovascular adverse effect profile. One of the largest trials, the CASTOR trial that included 283 and 286 patients in the VRd and D-VRd arms respectively reported few cardiovascular side effects; two patients with atrial fibrillation in both arms, one patient with acute coronary syndrome among others in the D-VRd arm that could not reach statistical significance given low sample size[11]. However, a comprehensive study investigating the cardiovascular profile of the new antimyeloma therapy is lacking. Therefore, we sought to utilize FAERS database to analyze the reported cardiovascular adverse events of the newly approved multiple myeloma therapies since 2015.

Methods:

Study Design and Data Collection

This is a retrospective, pharmacovigilance study of adverse event analysis of the U.S. Food and Drug Administration's Adverse Event Reporting System (FEARS) database. FAERS is an online publicly available post-marketing pharmacovigilance database that records millions of adverse events, medication error reports, and product quality complaints submitted by healthcare professionals, manufacturers, and consumers worldwide for approved drugs and biologic products. Reports are evaluated by clinical reviewers in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. The database includes data regarding the suspected pharmaceutical agent, indication for its use, patient characteristics, as well as the reported adverse event including its date of occurrence, nature, and outcome, among others. Since the data is anonymized, approval by an ethics committee (i.e. IRB approval) was not required for this analysis. We aimed to evaluate the cardiovascular adverse events associated with newly FDA-approved multiple-myeloma therapeutic agents from the approval till May 2021. Queries for the specific adverse event terms were performed according to the Medical Dictionary for Regulatory Activities. The terms used include "atrial fibrillation", "congestive cardiac failure, cardiac failure congestive", "ventricular dysfunction", "systolic dysfunction"; "diastolic dysfunction", "cardiac disfunction", "cardiac failure", "cardiomyopathy", "myocardial infarction", "angina pectoris", "coronary artery disease", "coronary artery occlusion", "angina unstable", silent myocardial infarction, "acute coronary syndrome" and were organized in these main groups.

Statistical Analysis

Statistical testing to measure the association of these drugs with the specified cardiac events of interest was performed using disproportionality signal analysis. These were presented as reporting odds ratios (RORs) of reported cardiac adverse events concomitant with the use of a newly approved multiple myeloma agent compared to the same reported adverse events within the entire database of pharmaceuticals within FAERS. The ROR was considered significant when the lower limit of the 95% CI was >1.0.

	Drug of interest	All other drugs in FAERS
Reports of AE of interest	A	B
All other AEs	C	D

ROR: AxD / BxC

Results:

The total number of adverse events (AEs) from all drugs in the FAERS database was over 20 million. Of those, the total number of AEs caused by the newly-approved therapeutic agents for multiple myeloma (including in combination with other medications) evaluated in this study was 30,797. Ixazomib had the highest number of total reported AEs with 13,701, followed by daratumumab with 10,235, while belantamab mafodotin had the lowest with 351 AEs. Out of the 30,797 AEs reported, 1131 were cardiac AEs. These included heart failure, atrial fibrillation, and coronary artery disease. Heart failure was reported the most with 470 AEs, while atrial fibrillation came next with 346, and coronary heart disease with 315. Ixazomib

had the highest reported heart failure and coronary heart disease AEs with 189 and 145 AEs respectively. Daratumumab had the highest atrial fibrillation AEs at 164 [Table 1].

Next, we analyzed the characteristics of the cardiac related AEs associated with elotuzumab, ixazomib, daratumumab, panobinostat, selinexor, and belantamab mafodotin. Since very few cardiac AEs reported for selinexor, and belantamab mafodotin, further analysis was not conducted for these medications [supplemental tables 5-6]. The majority of cardiac AE was among patients belonged to 65-85 age group (>55-59%), except, panobinostat which affected 40% of that age group. Overall, almost all of these cardiac AEs reported were serious (98%-100%). Consistently, the death rate was 25%-35% among cardiac adverse events on patients received elotuzumab, ixazomib, daratumumab. However, panobinostat reported the least mortality (3.5%) consistent with its relatively lower cardiac AEs on the older patients. However, more than one third of panobinostat-related reported cardiac AEs are not age specified [table 2 and supplemental tables 1-6]. Finally, gender biased-cardiac AEs are relatively higher among males, however, the results are not clear considering multiple reports were labeled as non-specific [table3].

The data was presented as reporting odds ratios (RORs) of reported cardiac adverse events concomitant with the use of a newly approved multiple myeloma agent compared to the same reported adverse events within the entire database of pharmaceuticals within FAERS. Atrial fibrillation and coronary heart disease were mostly associated with the use of panobinostat with ROR of 5.7 (95% CI: 4.1-8.1, P<0.0001) and 4.6 (95% CI: 3.8-8.1, P<0.0001) and elotuzumab with ROR of 5.8 (95% CI: 4.4-7.7, P<0.0001) and 2.7 (95% CI: 1.9-3.9, P<0.0001) respectively. Coronary artery disease had the lowest ROR with all agents with odds ratio between 2.3-4.6. Heart failure was reported the most with the use of elotuzumab with ROR of 8.2 (95% CI: 6.4-10.5, P<0.0001), while ixazomib exhibited the least association with ROR of 4.7 (95% CI: 4.1-5.4, P<0.0001). Of note, panobinostat's and daratumumab's ROR values were closely related compared to other agents [Figure 1 A-C and Table 4].

Discussion :

The results of this study demonstrated an association between the use of the newest novel multiple myeloma agents and cardiotoxicity. Among all of the adverse events reported for these new agents on FAERS, cardiac complications represented little less than 10%. Of all of the newly FDA approved multiple myeloma agents, elotuzumab, Ixazomib, daratumumab, panobinostat showed significant cardiac adverse events. Interestingly, cardiac failure, atrial fibrillation and coronary artery diseases were profoundly the highest of all reported cardiotoxicity. Interestingly, Isatuximab and belantamab mafodotin showed safer cardiac profile compared to elotuzumab, Ixazomib, daratumumab, panobinostat.

The fascinating ELOQUENT trials showed that elotuzumab significantly reduced multiple myeloma progression. Unspecified cardiac adverse events were reported among 7 patients with one death from heart failure with no concerning effects on QT prolongation[12,13]. The TOURMALINE trials that demonstrated the efficacy of Ixazomib on multiple myeloma reported similar adverse cardiac events (heart failure, myocardial infarction and arrhythmia) between the Ixazomib and the placebo group[14-16]. Three cases of myocardial infarction reported with panobinostat compared to placebo group[17]. Additionally,17.6% of patient who received panobinostat and bortezomib and dexamethasone reported cardiac complications (most frequently atrial fibrillation, tachycardia, palpitation, and sinus tachycardia) on phase 3 PANORAMA-1 trial[18]. Interestingly, no major cardiac adverse events reported associated with daratumumab[11,19].

While the study demonstrated undefined cardiovascular complications for new antimyeloma therapy, future studies are needed to investigate the underlying biological mechanisms driving this association. Moreover, prior cardiovascular functioning and other cardiac disorders were not considered while performing this study. Additionally, it is also important to state that FAERS-based studies typically examine association and not causality. Utilizing passive surveillance systems such as FAERS poses several limitations that pertain to this study including reporting bias, inaccuracy, and incompleteness of adverse events reports. The wholistic profile of patients (co-morbidities, risk factors, family history, etc.) are unknown. Moreover, it is important to note that pre-existing cardiovascular comorbidities including cardiac dysfunction and arrhythmias are specifically

common within age groups with the most reported adverse events[20]. Furthermore, multiple myeloma can worsen age-related cardiac dysfunction. In general, multiple myeloma is the third most common type of malignancy associated with cardiovascular disease, hence, the disease may have contributed to the reported adverse events[21]. For example, cardiac amyloidosis is frequently seen in multiple myeloma patients which can lead to cardiac dysfunction. Arrhythmias such as atrial fibrillation, paroxysmal ventricular tachycardias, and atrial flutter are well-reported in patients with multiple myeloma which are believed to be secondary to multi-factorial arrhythmogenesis secondary to age, electrolyte disturbances, and cardiac amyloidosis[22]. Due to these limitations, our results should be taken in consideration after further prospective, longitudinal studies have been performed.

Older therapeutic agents used in the treatment of multiple myeloma have been implicated in a plethora of cardiovascular adverse events. For example, doxorubicin is associated with a dose-related and usually irreversible Type I cardiac dysfunction that is thought to be related to excess generation of reactive oxygen species (ROS)[23]. The use of other major proteasome inhibitors including bortezomib and carfilzomib is associated with congestive heart failure and reversible cardiac dysfunction secondary to structural mitochondrial abnormalities and decreased nitric oxide levels with endothelial dysfunction, respectively Cardiac arrythmias associated with commonly used therapeutic agents have been well established in literature. For example, melphalan, doxorubicin, and cyclophosphamide are mainly associated with atrial fibrillation[29-33], while thalidomide and bortezomib are associated with bradycardia and complete heart block [22,34].

The significance of our data stems from the increasing use of new agents for multiple myeloma. As addressed above, multiple clinical trials showed sporadic cardiac adversaries of the novel multiple myeloma agents, however, a more thorough investigation of the cardiovascular profile of these medications is lacking. Our study strongly agrees with the aforementioned studies and showed enhanced cardiotoxicity especially atrial fibrillation, coronary artery disease and heart failure. Based on our results, we recommend physicians to discuss the cardiovascular risk with patients upon starting these medications. Electrocardiography and echocardiogram maybe help establish baseline cardiac function prior initiating these regimens.

In conclusions, novel multiple myeloma agents are associated with enhance atrial fibrillation, coronary artery disease and heart failure. Patient risk stratification and baseline cardiac functioning testing (electrocardiography and echocardiogram) should be considered upon initiating these agents.

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Author Contributions

All the authors contributed to the study design, writing and analysis. Data collection and analysis [Zaki Al-Yafeai, Anil Ananthaneni, Mohamed Ghoweba], design [Zaki Al-Yafeai, Hamzah Abduljabar, David Aziz]. The first draft was written by [Zaki Al-Yafeai] with edits and revision from all the authors. All authors read and approved the manuscript.

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