Myeloma and amyloid

Anne Blaes, MD, MSc[1], Douglas Sawyer, MD, PhD[2], Daniel Lenihan, MD[3]

[1] University of Minnesota, Division of Hematology, Oncology and Transplantation, United States
[2] Maine Medical Centre, Division of Cardiology, United States
[3] Vanderbilt University, Division of Cardiology, United States


Received: 7.12.2015. Accepted: 3.02.2016.

At the GCOS meeting in Nashville there were several important presentations about the treatment of myeloma and amyloidosis that have implications about cardiovascular conditions encountered with these hematologic malignancies. Session 9 began with Dr Paul Richardson highlighting the improvements in the treatment of myeloma. In the last 15 years, the overall survival of individuals diagnosed with multiple myeloma has increased dramatically. Recent data suggest that those with a diagnosis of multiple myeloma prior to 2001 had a median overall survival of 2.5 years as compared to a median overall survival of more than 6 years in those diagnosed between 2006–2010 [1]. Additionally, a recent international study reported three year survival rates after autologous stem cell transplantation of 88% [2]. Multiple myeloma therapy has changed dramatically in the last decade with new treatment options such as thalidomide, bortezomib and lenalidomide [3, 4], as well as advancements in supportive care, risk stratification, and the adoption of earlier treatment for those with high risk disease. More recently, multiple new drug therapies have also been developed including carfilzomib [5], pomalidomide [6], panobinostat [7], and the recently approved elotuzumab [7], with the anticipation that several more including daratumumab and ixazomib will soon be available.

With advancements in the field of multiple myeloma utilizing proteasome inhibitors, both reversible (bortezomib) and irreversible (carfilzomib), the question of cardiac safety has been raised. An outstanding presentation by Alexander Lyon, MD highlighted these potential concerns. The proteasome is the cell's protein 'garbage truck'. Proteins in the body are degraded through the process of ubiquitination. The ubiquitinated protein enters the proteasome and undergoes degradation into peptides. The balance of protein synthesis and degradation are essential in cardiac atrophy and cardiac hypertrophy [8]. Animal models suggest that chronic proteasome inhibition lead to both functional and structural alterations in the heart, consistent with a hypertrophic restrictive cardiomyopathy phenotype [9, 10]. To compound the problem in multiple myeloma where proteasome inhibitors are used, most individuals

Correspondence:
Anne Blaes, MD, MSc
University of Minnesota
Division of Hematology, Oncology and Transplantation
420 Delaware Street, SE, MMC 480
Minneapolis, MN 55455
tel.: 612-626-8138
e-mail: blaes004@umn.edu

using these medications have a high baseline risk of cardiovascular disease from prior cardiovascular disease, hypertension and advanced age. While two initial trials using bortezomib report dyspnea rates and edema rates as high as 15% and 20%, respectively [3], a recent metaanalysis of cardiac outcomes and the reversible proteasome inhibitor bortezomib [11] reported all grade cardiovascular toxicity rates of 3.8% (2.6–5.6) with no increase in cardiovascular events in those who used bortezomib as compared to those who did not. With the irreversible proteasome inhibitor carfilzomib, however, phase 3 clinical trials report cardiac adverse events (AEs) in 26% of the subjects as compared to 15% of the controls (11.4% vs. 5.7% grade 3 or higher AEs, respectively) [12]. Other single center experiences report cardiac toxicity in as many as 20% of individuals using carfilzomib [13, 14]. There is ongoing work in this area given several of these reports are limited by subjectivity and lack of specialist review. It is clear that surveillance and close monitoring is required in these situations.

The treatment of amyloidosis has also undergone a quiet resurgence in recent years. Dr Frank Cornell outlined how these treatments have developed and what anticipated toxicities may be. Amyloidosis is a serious disease characterized by an overproduction of misfolded immunoglobulin light chain protein leading to the extracellular deposition of amyloid fibrils in organs. Over 50% of patients with amyloid have cardiac involvement. Cardiac AL amyloid has a poor prognosis with only about half of patients surviving one year. Given the systemic plasma cell dyscrasia, heart transplantation is limited. The goal of treatment using chemotherapy or autologous stem cell transplantation (ASCT) is to eradicate the plasma cell clone and reduce the serum free light chains. With the proteasome inhibitors, partial or complete responses have been observed in 83% of those using a bortezomib based therapy as compared to 29% using a non-bortezomib-based therapy. More than half of the subjects in the bortezomib-containing arm had improvements in cardiac function with improvements in ejection fraction (EF), and reductions in brain natriuretic peptide level (NT-proBNP) [15]. Recent analyses looking at outcomes through the Center for International Blood and Marrow Transplant Research (CIBMTR) have also shown that post-transplantation survival in amyloidosis is improving with 5-year overall survival to 77% for those transplanted between 2007 and 2012 [16]. Prior to the use of bortezomib, many subjects with amyloidosis were excluded from ASCT. With the use of the proteasome inhibitor bortezomib, it appears that bortezomib-based induction for transplant-ineligible individuals with amyloidosis can actually make ASCT feasible [17]. Predictors of a poorer outcome with transplant have been identified and transplant is generally not recommended for those with the following characteristics: NT-proBNP of > 8500 pg/ml, systolic blood pressure < 100 mmHg [18], creatinine > 2 g/dl. Given the potential cardiac toxicity with the irreversible proteasome inhibitor carfilzomib, its use in patients with cardiac amyloid is not currently recommended. Finally, there are new therapies in development for amyloidosis including a humanized IgG1 monoclonal antibody, NEOD001, directed at a cryptic epitope exposed on immunoglobulin light chain protein only when part of the amyloid fibril [19], that hopefully will continue to impact the survival of patients with amyloidosis.

With advancements in multiple myeloma and amyloidosis and newer targeted therapies affecting the proteasome pathway, it is imperative that cardiologists and hematologists/oncologists collaborate in the care of these patients. Many individuals with multiple myeloma and amyloid have underlying cardiovascular risk factors including prior cardiac disease and hypertension. A baseline risk assessment looking at cardiovascular disease, prior anthracycline use, hydration status, and concurrent medications should take place. Cardiac surveillance should be considered using NT-proBNP, troponin, and echocardiogram. Consideration on the cardiac impact of chemotherapy drugs such as carfilzomib should also take place. Additionally, further research is needed in this area particularly to examine the true cardiac impact of medications such as carfilzomib, as well as to examine the usefulness and timing of surveillance.

Acknowledgements

The presented report is the summary of the session 9 of the **Global Cardio-Oncology Summit**, organized in Nashville, Tennessee, US (October, 15–16th, 2015).

References

1. Kumar SK, Dispenzieri A, Lacy MQ et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014; 28(5): 1122-1128.
2. Attal M, Lauwers-Cances V, Hulin C et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone du Myelome (IFM/DFCI 2009 Trial). Blood 2015; 126(23).
3. Richardson PG, Sonneveld P, Schuster MW et al. Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352(24): 2487-2498.

4. San Miguel JF, Schlag R, Khuageva NK et al. VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008; 359(9): 906-917.
5. Stewart AK, Rajkumar SV, Dimopoulos MA et al. ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015; 372(2): 142-152.
6. Shah JJ, Stadtmauer EA, Abonour R et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. Blood 2015; 126(20): 2284-2290.
7. Laubach JP, Moreau P, San-Miguel JF, Richardson PG. Panobinostat for the treatment of multiple myeloma. Clin Cancer Res 2015; 21(21): 4767--4773.
8. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction – Alzheimer's disease of the heart? N Engl J Med 2013; 368(5): 455-464.
9. Herrmann J, Wohlert C, Saguner AM et al. Primary proteasome inhibition results in cardiac dysfunction. Eur J Heart Fail 2013; 15(6): 614-623.
10. Ranek MJ, Zheng H, Huang W et al. Genetically induced moderate inhibition of 20S proteasomes in cardiomyocytes facilitates heart failure in mice during systolic overload. J Mol Cell Cardiol 2015; 85: 273-281.
11. Xiao Y, Yin J, Wei J, Shang Z. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: A systematic review and meta-analysis. PLoS One 2014; 9(1): e87671.
12. Siegel D, Martin T, Nooka A et al. Integrated safety profile of single-agent carfilzomib: Experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013; 98(11): 1753-1761.
13. Atrash S, Tullos A, Panozzo S et al. Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. Blood Cancer J 2015; 5: e272.
14. Danhof S, Schreder M, Rasche L et al. 'Real-life' experience of preapproval carfilzomib-based therapy in myeloma – analysis of cardiac toxicity and predisposing factors. Eur J Haematol 2015 [doi: 10.1111/ejh.12677; epub ahead of print].
15. Sayago I. Impact of proteosomal inhibitors on cardiac AL amyloid. Heart Failure Association 2015 Summer Congress.
16. D'Souza A, Dispenzieri A, Wirk B et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: A center for international blood and marrow transplant research study. J Clin Oncol 2015; 33(32): 3741-3749.
17. Cornell RF, Zhong X, Arce-Lara C et al. Bortezomib-based induction for transplant ineligible AL amyloidosis and feasibility of later transplantation. Bone Marrow Transplant 2015; 50(7): 914-917.
18. Wechalekar AD, Schonland SO, Kastritis E et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013; 121(17): 3420-3427.
19. Wall JS, Kennel SJ, Williams A et al. AL amyloid imaging and therapy with a monoclonal antibody to a cryptic epitope on amyloid fibrils. PLoS One 2012; 7(12): e52686.