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Cardiovascular Issues in Multiple Myeloma: Clinical Implications of the Double Burden of Treatment and Immunoglobulin Light Chain Amyloidosis: A Narrative Review

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ABSTRACT

Multiple myeloma (MM) represents about 0.9% of global cancer cases, with a steadily rising incidence. As the treatment landscape for MM continues to develop, with a growing range of therapeutic options. Advances in MM treatment have improved patient outcomes. However, cardiovascular (CV) complication risk has emerged as a major concern. Patients with MM are at increased risk for CV complications secondary to advanced age and disease-related symptoms such as renal impairment, anemia, and hyperviscosity syndrome. Moreover, MM patients also face a heightened risk of thrombosis. CV complications among MM patients are associated with patient-specific factors, MM-related factors, and treatment-related toxicity. Treatment-Related Factors: proteasome inhibitor, immunomodulatory drugs, chimeric antigen receptor T-cell therapy, bispecific antibodies, transplantation, etc. Understanding the specific CV complications associated with each therapeutic agent and their potential onset is also essential. Prior to initiating treatment, assessing the risk of CV complications is crucial to enhance patient safety and minimize treatment-related adverse events, which have a prognostic impact.

Another critical issue in CV complications is cardiac amyloidosis (CA) resulting from immunoglobulin light chain (AL) amyloidosis, which often coexists with MM and leads to a significant burden of disease. Early detection of CA allows targeted therapeutic strategies to be applied, ultimately improving patient outcomes. Diagnostic efforts should focus on identifying findings suggesting amyloidosis and confirming the diagnosis through comprehensive assessments. It is important to keep in mind that heart failure and arrhythmias account for a significant proportion of early deaths in MM patients with CA. Treatment for CA primarily involves two approaches: managing heart failure and reducing light chain production.

1. Introduction

Multiple myeloma (MM) accounts for approximately 0.9% of all cancer diagnoses worldwide. In 2018, it was estimated that there were 160,000 MM patients globally. Notably, the global incidence of MM increased by 126% between 1990 and 2016. [1]

The treatment landscape for MM continues to develop, with a growing range of therapeutic options. The Food and Drug Administration (FDA) has approved several treatments, including thalidomide, bortezomib, and lenalidomide. Over the past decade, additional therapies have been introduced, such as carfilzomib, pomalidomide, ixazomib, elotuzumab, daratumumab, isatuximab, selinexor, belantamab mafodotin, teclistamab, talquetamab, elranatamab, and chimeric antigen receptor T cell therapy. [2]

Although advances in MM treatment have improved patient outcomes, certain therapeutic agents can adversely affect the cardiovascular (CV) system. Additionally, the prevalence of CV disease increases with age. [3] MM primarily affects elderly individuals, with a median age at diagnosis of 69 years in the United States. Over 60% of cases are diagnosed in individuals aged 65 or older, whereas fewer than 15% of diagnoses occur in those under the age of 55. [1] Consequently, MM patients face a high risk of CV complications due to advanced age. Moreover, patients with MM frequently present with symptoms such as renal impairment, anemia, and hyperviscosity syndrome, which are associated with CV complications. Additionally, MM patients are at a high risk of developing thrombosis. Importantly, CV complications negatively impact prognosis, as patients who experience CV adverse events exhibit poorer progression-free and overall survival.[4]

Therefore, the risk of CV complications has emerged as a major concern in the treatment of MM. It is essential to understand the specific CV complications associated with each therapeutic agent and their potential onset time and assess the risk prior to initiating treatment.

Another critical issue in CV complications is cardiac amyloidosis (CA) resulting from immunoglobulin light chain (AL) amyloidosis, which often coexists with MM and leads to a significant burden of disease. The survival of patients with systemic AL amyloidosis largely depends on the severity of CA at diagnosis. [5] Early detection of CA allows targeted therapeutic strategies to be applied, ultimately improving patient outcomes. Diagnostic efforts should focus on identifying findings suggesting amyloidosis and confirming the diagnosis through comprehensive assessments. It is important to keep in mind that heart failure and arrhythmias account for a significant proportion of early deaths in MM patients with CA.[6]

Recognizing, understanding, and managing CV issues in MM is essential for improving patient outcomes. Clinicians need to be aware of these risks and integrate appropriate strategies into their clinical practice. To address this issue, we conducted a narrative review of CV issues associated with MM.

This review aims to provide a comprehensive overview of CV issues related to MM, with the goal of increasing awareness among healthcare professionals. The scope of this review is emphasized by the dual impact of therapeutic agents and AL amyloidosis. It addresses the following key areas: integrated CV risk assessment and management, therapy-related CV complications, and CA.

2. Cardiovascular Issues Associated with Multiple Myeloma Treatments

2.1. General Issues Cardiovascular Complications Associated with Treatment

Therapy-related CV complications among MM patients undergoing treatment include accelerated hypertension, ischemic heart disease, congestive heart failure, arrhythmias, pulmonary hypertension, venous thromboembolism, arterial thromboembolism, etc.[7,8]

The risk factors contributing to CV complications can be classified into three main categories [9,10]:

1. MM-Related Factors: renal impairment, anemia, hyperviscosity, and AL amyloidosis.
2. Patient-Specific Factors: preexisting heart disease, older age, male sex, obesity, black ethnicity, hypertension, diabetes, and dyslipidemia.
3. Treatment-Related Factors: proteasome inhibitor, immunomodulatory drugs, chimeric antigen receptor T-cell therapy, bispecific antibodies, and transplantation, etc.

Particular therapies may further exacerbate CV risk when combined with MM-related and patient-specific factors. Therefore, a baseline CV risk assessment should be conducted to evaluate risks associated with MM and patient-specific factors. Subsequently, an assessment of treatment-related risks is also necessary.

2.2. BASELINE CARDIOVASCULAR RISK ASSESSMENT

A comprehensive baseline CV risk assessment is essential. The current guidelines [11,12] provide a baseline CV risk assessment.

This includes:

- Medical History: previous chemotherapy exposure, history of CV disease, and known CV risk factors.
- Basic Cardiac Evaluations: electrocardiogram (ECG) and echocardiography for all patients.
- Additional Assessments for High-Risk Patients:
  - Cardiac Biomarkers: B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac troponin for dynamic monitoring.
  - Metabolic Profile: lipid profile, fasting plasma glucose, and HbA1c if metabolic risk factors are present.

Early identification of CV risk factors and awareness of treatment-related complications allow for preventive strategies, including appropriate consultations with cardiologists. Implementing these measures can help reduce the incidence of CV complications in MM patients undergoing treatment. [8]

The following sections outline specific CV complications associated with MM therapies.

2.3. PROTEASOME INHIBITOR

Proteasomes are large, multicatalytic protein complexes. They play a degradative role and contribute to over 80% of protein turnover. Proteasomes function through the NF-κB signaling pathway, cellular tumor antigen p53, cyclins, cyclin-dependent kinases, and other regulatory proteins. Proteasome inhibitors are an essential class of therapeutic agents for MM. The primary mechanism of action of proteasome inhibitors is the inhibition of the proteasome, thereby disrupting protein homeostasis in MM cells. Bortezomib was the first proteasome inhibitor approved by the FDA, followed by the approvals of carfilzomib and ixazomib. [13]

Cardiovascular Events Associated with Bortezomib

A systematic review and meta-analysis examined data from January 1, 1966, to July 31, 2013, assessing CV events such as left ventricular ejection fraction decline, chronic heart failure, cardiomyopathy, cardiac arrest, and arrhythmia. The analysis included 5,718 patients, with reported incidences of all-grade cardiotoxicity ranging from 0% to 17.9%. However, bortezomib use did not significantly increase the risk of all-grade cardiotoxicity (odds ratio [OR]: 1.15, 95% confidence interval [CI]: 0.82–1.62, $p = 0.41$) or high-grade cardiotoxicity (OR: 1.13, 95% CI: 0.58–2.24, $p = 0.72$) compared to control treatments. [14] Therefore, bortezomib use may not be associated with an increased incidence of CV complications.

Cardiovascular Events Associated with Carfilzomib

A systematic review and meta-analysis evaluated the cumulative incidence of CV events associated with carfilzomib among 4,164 patients. The estimated incidence of all-grade and high-grade (≥ grade 3) cardiotoxicity was 8.68% and 4.92%, respectively. Compared to control groups, carfilzomib use was associated with a significantly higher risk of CV events, with an OR of 2.03 (95% CI: 1.19–3.46, $p = 0.010$) for all-grade events and 2.04 (95% CI: 1.31–3.17, $p = 0.002$) for high-grade events. [15]

A prospective observational study assessed CV adverse events in 95 patients with relapsed MM treated with proteasome inhibitors. Among them, 65 received carfilzomib, while 30 received bortezomib. CV adverse events occurred in 51% of patients treated with carfilzomib, compared to 17% of those receiving bortezomib. The median time from treatment initiation to the first CV event was 31 days (ranged 0–151 days). Heart failure was the most common CV event in patients receiving carfilzomib (35%), followed by grade 3 or 4 hypertension (20%). Additionally, 13% of patients experienced cardiac chest pain, 3% developed atrial fibrillation, and 4% experienced acute coronary syndrome.[4] Thus, carfilzomib use was associated with an increase in CV events.

Cardiovascular Events Associated with Ixazomib

A previous phase 3 clinical trial assessed the safety and efficacy of ixazomib in patients with relapsed and refractory MM. Participants received either an ixazomib-lenalidomide-dexamethasone regimen or a placebo-lenalidomide-dexamethasone regimen. The incidence of CV complications in the ixazomib group was as follows: arrhythmias occurred in 16% of patients, thromboembolism in 8%, hypertension in 6%, and hypotension in 6%.[16] However, case reports have documented acute decompensated heart failure possibly associated with ixazomib use. [17] Although heart failure may occur, it appears to be infrequent.

2.4. IMMUNOMODULATORY DRUGS

Immunomodulatory drugs (IMiDS) exhibit several anti-myeloma activities, including immune system modulation, cytokine release modification, anti-angiogenic effects, etc.

The following sections describe these mechanisms in more detail.

- The modulation of the immune system
  IMiDs have been shown to modulate immune system components by altering cytokine production, regulating T-cell co-stimulation, and enhancing NK cell cytotoxicity. IMiDs directly stimulate T cells and increase Th1-type cytokines. In addition, IMiDs enhance the activity of cytotoxic T lymphocytes and NK cells against MM. [18,19]
- Modification of Cytokine Release
  IMiDs have been shown to inhibit the production of cytokines, including TNF-α, IL-1, IL-6, IL-10, and IL-12. Notably, the downregulation of TNF-α secretion is particularly pronounced. These changes in cytokine release are thought to contribute to the apoptosis of MM cells. [19]
- Anti-angiogenesis activity
  IMiDs have been shown to significantly reduce the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and Interleukin-6, in MM. This reduction may decrease angiogenesis, thereby contributing to the efficacy of IMiDs in MM. [19]

Multiple Myeloma Patients are at High Risk of Thrombosis

Patients with MM face a heightened risk of thrombosis, which negatively impacts prognosis. A Swedish study examined this risk among 18,627 MM patients diagnosed between 1958 and 2006, comparing them with matched controls. The hazard ratios (HRs) for venous thromboembolism (VTE) among MM patients, relative to controls, were 7.5 (95% CI, 6.4–8.9) at 1 year, 4.6 (95% CI, 4.1–5.1) at 5 years, and 4.1 (95% CI, 3.8–4.5) at 10 years post-diagnosis. [20]

Furthermore, thrombosis adversely affects survival in MM patients. A study of 9,399 MM patients diagnosed in Sweden between 1987 and 2005 found that those who developed thrombosis after diagnosis had higher mortality rates than those without thrombosis at 1-, 5-, and 10-year follow-ups. The HRs for mortality were 3.4 (95% CI: 3.0–3.8) at one year, 2.1 (95% CI: 2.0–2.2) at five years, and 2.0 (95% CI: 1.9–2.2) at ten years. [21] Thus, patients with MM are at high risk for thrombosis, which is a critical issue with prognostic implications and should be kept in mind by the clinician. The following paragraphs discuss thrombosis in the treatment of patients with MM.

Immunomodulatory Drugs and Thrombosis Risk

In 2008, the International Myeloma Working Group (IMWG) proposed consensus-based guidelines for thromboprophylaxis in MM patients treated with IMiD. Risk factors associated with VTE include MM-related, Patient-specific, and Treatment-related factors. [22] Daily low-dose aspirin (81–325 mg) is recommended when there are no risk factors or only one. In the presence of two or more risk factors, low-molecular-weight heparin (e.g., enoxaparin 40 mg once daily) or full-dose warfarin (target international normalized ratio [INR] of 2–3) is advised. [22]

Notably, the details of treatments given to MM patients were reported. [23] According to this report, when assessing the risk of VTE, physicians commonly take into account factors such as comorbidities, patient history, and MM disease characteristics. Regarding the duration of thromboprophylaxis in cases where IMiD-based therapy is selected, 70.9% of clinicians continue thromboprophylaxis until the completion of IMiD-based treatment. Direct oral anticoagulants (DOACs) were the most preferred antithrombotic agents for thromboprophylaxis, regardless of patient age or concomitant VTE risk factors. Low-molecular-weight heparin was preferred for patients with VTE risk factors. Aspirin has a tendency not to be used when patients have risk factors for VTE. [23]

2.5. CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

Chimeric antigen receptor T (CAR-T) cell therapy is an advanced immunotherapy that involves genetically engineering T cells to target specific antigens on tumor cells. The CAR molecule consists of two primary domains: an extracellular single-chain antibody domain and an intracellular signaling domain. The extracellular domain recognizes and binds to the target antigen, while the intracellular signaling domain—linked through a hinge region and transmembrane domain—transmits an activation signal. This activation prompts the T cells to attack the target cells selectively.

The process of generating CAR-T cells begins with the collection of T cells from the patient. These cells are then genetically modified to express the CAR protein on their surface, enabling them to recognize and target tumor-specific antigens. Following this modification, the T cells are expanded (cultured) in vitro and subsequently reintroduced into the patient.[24]

Cytokine Release Syndrome

According to the CTCAE v5.0, cytokine release syndrome (CRS) is defined as a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia resulting from cytokine release. [25] The CV manifestations of CRS include tachycardia, hypotension, left ventricular dysfunction, arrhythmias, cardiogenic shock, and pulmonary edema. Additionally, elevated troponin levels and other abnormal laboratory findings may indicate myocardial injury.

Cardiotoxic effects may be transient and reversible in younger patients with no serious cardiac comorbidities, whereas they may be severe or even fatal in older patients with significant pre-existing cardiac risk factors. [26]

CAR-T Associated Cardiovascular Events Among Multiple Myeloma Patients

Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen (BCMA)-directed CAR-T therapy for MM patients. According to a randomized, patients with lenalidomide-refractory MM assigned to receive cilta-cel or the physician's choice of effective standard care. Among the patients in the as-treated population who received cilta-cel, 76.1% developed CRS, with 1.1% experiencing grade 3 or 4 CRS and no reported cases of grade 5 CRS. The median time to CRS onset was 8 days (ranged 1–23 days), with a median duration of 3 days (range: 1–17 days). There were no patients with CRS (grade 3–4) in the study who exhibited CA manifestations secondary to CRS. [27] Therefore, CV events may not be a frequent complication of CAR-T therapy in MM patients.

2.6. BISPECIFIC ANTIBODIES

Bispecific antibodies (BsAbs) are engineered antibodies that contain two distinct antigen-binding sites within a single molecule. They can simultaneously bind to a tumor-specific antigen and the T-cell CD3 co-receptor. In MM treatment, key target proteins for BsAbs in the treatment of MM include B-cell maturation antigen, BCMA G-protein-coupled receptor family C group 5 member D (GPRC5D), and Fc receptor-homolog 5 (FcRH5). When BsAbs bind to the tumor antigen, BsAbs activate T cells, triggering degranulation and membrane perforation of the target cell. This process induces apoptosis through the action of perforin and granzyme B. [28]

Bispecific Antibodies Associated Cardiovascular Events

Common adverse events associated with BsAbs include infections, cytopenias, CRS, and neurological toxicities. Across clinical trials of BsAbs, CRS has been reported in a significant proportion of patients, with an incidence ranging from 46.3% to 82.4% for all grades. However, the occurrence of grade ≥3 CRS remains low, ranging from 0% to 3%. [28]

Current Use of Bispecific Antibodies

Teclistamab is a T-cell-redirecting BsAb that targets both CD3, expressed on the surface of T cells, and BCMA. In the phase 1–2 study among patients with relapsed or refractory MM who received weekly subcutaneous injections of teclistamab (1.5 mg per kilogram of body weight) following step-up doses of 0.06 mg and 0.3 mg per kilogram. Among patients who received teclistamab, CRS occurred in 72.1% of patients, grade 3 in 0.6%, and no grade 4 cases. Notably, no CV complications due to CRS were observed. [29] CV event may not be a frequent adverse event in the BsAbs use in patients with MM.

2.7. TRANSPLANTATION

Melphalan-Induced Supraventricular Tachycardia

A retrospective study analyzed data from patients who underwent hematopoietic stem cell transplantation between 1998 and 2005. Among the patients who received high-dose melphalan as part of their conditioning regimen, 11% developed atrial fibrillation, 7% experienced atrial flutter, and 3% developed other types of supraventricular tachycardia, including atrial tachycardia (2%) and atrioventricular nodal reentrant

tachycardia (2%).[30] Therefore, patients receiving high-dose melphalan should be closely monitored for the development of supraventricular tachycardia.

3. Cardiovascular Issues Associated with Patients with AL Amyloidosis

3.1. IMMUNOGLOBULIN LIGHT CHAIN AMYLOIDOSIS

Amyloidosis refers to a group of diseases caused by the misfolding of soluble precursor proteins. To date, 42 soluble precursor amyloidogenic proteins have been identified. [5] The primary causes of CA are AL amyloidosis and amyloid transthyretin amyloidosis, which together account for nearly all cases. A previous study examined 182 patients with CA and reported the following distribution: 47.3% had AL amyloidosis, 44.5% had amyloid transthyretin amyloidosis, and 8.2% had other etiologies. [31] Thus, AL amyloidosis accounted for almost half of all cases.

Amyloidosis is classified as systemic or localized, depending on whether multiple or a single organ is affected. AL amyloidosis is typically associated with plasma cell disorders. Immunoglobulin light chains primarily cause AL amyloidosis in most cases. Specifically, lambda light chains account for 75–80% of cases, while kappa light chains are responsible for the remaining 20–25%. In contrast, AL amyloidosis caused by immunoglobulin-heavy chains is much rarer. [5] In most cases, MM and AL amyloidosis are diagnosed simultaneously, typically within four months of each other. In only 1.5% of cases, MM is diagnosed after AL amyloidosis. [32]

3.2. PATHOGENESIS OF AL AMYLOIDOSIS.

In AL amyloidosis, clonal plasma cells secrete monoclonal antibodies into the bloodstream. These monoclonal antibodies are deposited on and damage tissues through two primary mechanisms.

Firstly, some light chains undergo misfolding, becoming "misfolded light chains." These aberrant proteins can be directly deposited in tissues, leading to damage. Additionally, they can trigger toxic cellular effects through the activation of p38 mitogen-activated protein kinase (MAPK) signaling and the generation of reactive oxygen species (ROS).

The second mechanism of tissue damage involves the repeated aggregation of misfolded light chains, leading to their deposition in tissues and subsequent damage. Misfolded light chains can aggregate by binding to one another and forming larger structures. Initially, a small number of these aggregates, known as "oligomers,". As this process progresses, oligomers further aggregate into larger, more stable structures called "cross-beta-pleated amyloid fibrils." The deposition of these fibrils in affected tissues causes damage.[5]

3.3. DIAGNOSIS OF CARDIAC AMYLOIDOSIS

The diagnosis of CA typically begins with clinical and/or imaging findings suggestive of amyloidosis. The most definitive method for diagnosing CA is a pathological assessment of a myocardial biopsy demonstrating amyloid deposition.[33] However, myocardial biopsy is an invasive procedure, which limits its widespread use. Therefore, diagnosis often involves an initial evaluation based on clinical and imaging findings, followed by confirmation through advanced imaging techniques, biochemical screening for monoclonal antibodies, and histological evaluation by biopsies. Tissue samples for biopsy may be obtained from alternative sites such as abdominal fat, salivary glands, gingiva, rectum, skin, or bone marrow. [5,34]

Patients with suspected CA should undergo a comprehensive assessment, including ECG, echocardiography, serum troponin measurement, and NT-proBNP testing. Notably, imaging techniques—particularly echocardiography and cardiac magnetic resonance imaging—play a crucial role in diagnosis. [35]

3.4. PRESENTATION OF CARDIAC AMYLOIDOSIS

Patients with CA often exhibit common symptoms of heart failure, including fatigue, dyspnea, reduced exercise tolerance, edema, and weight gain. [35] CA typically manifests as restrictive cardiomyopathy. [5,35] The cohort had a mean age of 73 years (range: 63–80) and was 67% male. Among them, 79 patients (44.6%) were classified as New York Heart Association (NYHA) class ≥ III. The mean systolic blood pressure was 120 mmHg (range: 110–140), and 10.4% experienced syncope. Hypertension was present in 54.4% of patients. The mean estimated glomerular filtration rate (eGFR) was 50 mL/min (range: 36–75), with 51% having an eGFR < 60 mL/min. Additionally, 6.6% of patients had ischemic heart disease, 36.7% had a history of atrial fibrillation, and 24.3% had carpal tunnel syndrome. [31]

3.5. ARRHYTHMIA IN PATIENTS WITH CARDIAC AMYLOIDOSIS

Patients with CA frequently develop arrhythmias, which are a major cause of early mortality. [36] Among newly diagnosed patients with AL amyloidosis, sudden cardiac death accounts for approximately one-third of deaths within the first 90 days. Bradyarrhythmia and conduction system disease may also contribute to sudden cardiac death in patients with CA. [36] Regarding ECG findings in CA, ECG may reveal low voltages and pseudo-infarct patterns in patients with CA. [35] A retrospective study of 182 patients with CA, including 47.3% with AL amyloidosis, reported the following ECG findings: sinus rhythm in 53.3%, atrial fibrillation in 40.2%, and pacemaker rhythm in 6.5%, with a median heart rate of 70 bpm (interquartile range: 65–85). Right bundle branch block was observed in 21.7%, left bundle branch block in 18.5%, and left anterior fascicular block in 20.7%. Additionally, pathological Q waves in 25% and low QRS voltages in 29.3%. [31]

3.6. FINDINGS OF ECHOCARDIOGRAPHY IN CARDIAC AMYLOIDOSIS

Echocardiography plays a crucial role in diagnosing CA. A key echocardiographic feature of CA is left ventricular hypertrophy (LVH) with a granular, sparkling myocardial texture, as seen on two-dimensional echocardiography. [35] However, it is important to note that while this granular sparkling appearance is a common finding in CA, it is not highly specific, as it can also be seen in other conditions, such as end-stage renal disease. [37] Another notable echocardiographic finding in CA is voltage-mass

mismatch, characterized by low voltages on ECG despite the presence of LVH on echocardiography. [35]

Additionally, a small pericardial effusion is frequently observed. In the apical four-chamber view, echocardiography often reveals increased biventricular wall thickness, biatrial enlargement, and thickening of both the interatrial septum and mitral valve leaflets. [35]

Tissue Doppler imaging and speckle-tracking echocardiography helps the non-invasive detection of CA. A hallmark feature of CA is a reduction in global longitudinal strain with apical sparing, which serves as an early marker of systolic dysfunction. It should be noted that left ventricular ejection fraction typically remains preserved until the later stages of the disease. [35,37]

In addition to echocardiography, cardiac magnetic resonance (CMR) is important in distinguishing CA from other cardiomyopathies associated with increased wall thickening. CMR can also facilitate the early detection of cardiac involvement in patients with systemic amyloidosis. A CMR evaluation for CA includes cine imaging, native T1 signal assessment using non-contrast T1 mapping, late gadolinium enhancement analysis, and extracellular volume measurement. [37]

3.7. TREATMENT OF PATIENTS WITH CARDIAC AMYLOIDOSIS

The treatment of AL cardiac amyloidosis primarily involves two approaches: managing heart failure and targeting the underlying plasma cell abnormalities responsible for amyloid production.

The management of heart failure requires collaboration among cardiologists, particularly in the management of heart failure secondary to AL amyloidosis, including the use of diuretics for sodium restriction. Angiotensin-converting enzyme (ACE) inhibitors should be administered to reduce afterload. In patients with recurrent syncope, a pacemaker may be required, while ventricular arrhythmias can be managed with amiodarone or implantable defibrillators.[5]

The primary therapeutic goal for AL amyloidosis is to reduce the production of light chains, which are the source of amyloid deposits. According to National Comprehensive Cancer Network (NCCN) guidelines [38], the recommended first-line treatment for AL amyloidosis is a combination of daratumumab with bortezomib, cyclophosphamide, and dexamethasone. Patients treated with this regimen achieved a hematologic complete response rate of 53.3%. At six months, cardiac responses were observed in 41.5% of patients. The four most common grade 3 or 4 adverse events included lymphopenia (13.0%), pneumonia (7.8%), cardiac failure (6.2%), and diarrhea (5.7%). [39]

3.8. PROGNOSIS AND CAUSES OF DEATH IN CARDIAC AMYLOIDOSIS

A previous study [6] reported that survival times for AL amyloidosis have improved over time. The study categorized 2,337 patients with AL amyloidosis into four groups based on their diagnosis period: 1980–1989 (Era 1), 1990–1999 (Era 2), 2000–2009 (Era 3), and 2010–2019 (Era 4). The results demonstrated a consistent increase in median survival times, which were 1.4, 2.6, 3.3, and 4.6 years for Eras 1 through 4, respectively ($P < 0.001$). Additionally, six-month mortality rates declined over time, from 23% in Era 1 to 13% in Era 4. [6]

This study also assessed 1,859 patients with CA based on predefined criteria. [40] Among these patients, the median overall survival improved across eras, increasing from 0.9 years (95% CI, 0.6–1.3 years) in Era 1 to 2.6 years (95% CI, 2.4–3.5 years) in Era 4. [6] Thus, these findings indicate that survival among patients with CA has improved over time. However, despite these advancements, the median survival of patients with CA remains relatively short at 2.6 years in Era 4. Notably, this is lower than the median survival of the entire cohort in Era 4, which is 4.6 years.

The identified causes of death were also reported as follows: organ failure (49%), including cardiac (32%), renal (11%), hepatic (3%), and autonomic failure (2%); sudden unexpected death (23%); infection (11%); treatment-related events (4%); major vascular events, such as stroke, myocardial infarction, and VTE (4%); hemorrhage (3%); malignancy (2%); and other causes (5%). [6] Notably, as the survival time from diagnosis increased, the percentage of deaths due to cardiac failure and sudden death decreased. [6] Thus, heart failure remains a major concern in AL amyloidosis, accounting for 32% of deaths and contributing to early mortality. Additionally, major vascular events represent 4% of treatment-related complications.

4. Conclusion

CV issues must be carefully assessed in patients with MM due to their significant prognostic impact. Advances in MM treatment have improved patient outcomes; however, as most MM patients are elderly, the disease frequently leads to symptoms such as renal impairment, anemia, and hyperviscosity syndrome. Additionally, MM patients are at a high risk of developing thrombosis. Before initiating treatment, assessing and managing the risk of CV complications is crucial to enhance patient safety and minimize treatment-related adverse events. Understanding the specific CV complications associated with each therapeutic agent and their potential onset is also essential.

In particular, CA should be carefully evaluated in MM patients, as early recognition is critical for timely intervention. Diagnostic efforts should focus on identifying findings suggesting amyloidosis and confirming the diagnosis through comprehensive assessments. It is important to keep in mind that heart failure and arrhythmias account for a significant proportion of early deaths in MM patients with CA. Treatment for CA primarily involves two approaches: managing heart failure and reducing light chain production. Early identification of CA enables the implementation of targeted therapeutic strategies, ultimately improving patient outcomes.

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