Cardiovascular Complications of Novel Multiple Myeloma Treatments

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**Case presentation:** A 75-year-old woman was referred to cardiology for optimization of cardiovascular risk factors before starting a new cancer treatment. She was diagnosed with IgG-κ multiple myeloma (MM) 2 years previously that progressed after her previous treatments. Her medical history also included type 2 diabetes mellitus, hypertension, and a remote history of deep vein thrombosis treated with a “blood thinner” for 6 months. Her hematologist has determined that a combination of carfilzomib, lenalidomide, and dexamethasone is the best treatment option for this patient but is concerned about the risk of cardiovascular complications from the new treatment and wants the patient to undergo evaluation by a cardiologist.

**Overview**

MM is a plasma cell malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction.1 MM accounts for 1% of all cancers and ≈13% of all hematologic malignancies. Approximately 86,000 new cases of MM occur annually worldwide and affect primarily older individuals with a median age of diagnosis of ≈70 years.2 Over the past few decades, overall survival has improved from an age-adjusted 5-year relative survival of 35.6% in 1998 to 2001 to 44% in 2006 to 2009.3 This improvement is due largely to increased use of autologous stem cell transplantation and the introduction of novel agents, including immunomodulatory drugs (IMiDs; ie, thalidomide [Thalomid], lenalidomide [Revlimid], and pomalidomide [Pomalyst]) and proteasome inhibitors (PIs; ie, bortezomib [Velcade] and carfilzomib [Kyprolis]). Figure 1 shows the milestones in MM treatment.

**Thrombosis and MM**

Cancer is associated with increased risk of venous thromboembolic events (VTEs).4 As early as 1868, Trousseau5 described the relationship between malignancy and venous thrombosis. A large case-control study has shown that malignancy by itself increases the risk of VTEs by 7- to 10-fold; hematologic malignancies, including MM, are especially associated with high VTE risk (up to 28-fold), representing the highest reported risk of VTEs among patients with cancer.6 A hypercoagulable state in MM was recognized in the early 1970s, and MM was described as an independent risk factor for VTEs.7 Before the introduction of IMiD therapy, ≈10% of patients with MM treated with chemotherapy experienced VTE complications, and the median time from diagnosis to the development of VTEs was 8.5 months.9 VTEs have increasingly been observed in patients with MM treated with IMiDs, especially when used in combination with high-dose dexamethasone or chemotherapy.10 Figure 2 demonstrates the proposed mechanisms of increased VTEs in MM.

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VTEs was again observed in later thalidomide trials and led to a protocol amendment that thromboprophylaxis would be initiated for patients receiving thalidomide-based regimens. Patients receiving dexamethasone, which was commonly given in combination with thalidomide, were at particularly high risk for VTEs. A meta-analysis of >3000 patients with MM showed that thalidomide increased the VTE risk by 2.6 times; when thalidomide was combined with dexamethasone, the VTE risk was increased by 8-fold. Lenalidomide and pomalidomide, potent derivatives of thalidomide, have also demonstrated increased propensity for VTEs. The incidence of VTEs associated with these agents was lower in trials with mandatory thromboprophylaxis (Table).

**Increased Arterial Thromboembolic Risk in MM**

Patients with MM also have a higher risk of arterial thromboembolic events (ATEs), including coronary artery disease and cerebrovascular disease. Increased risk might be due partially to a high burden of cardiovascular comorbidities in the older patient population. However, a prospective cohort study of younger patients with MM (age, 18–65 years) reported a high incidence of ATEs (5.6%), with a median age of onset of 59 years. Hypertension and smoking were significantly associated with ATEs, with a relative risk of 11.7 and 15.2, respectively. Thalidomide treatment was not associated with increased ATE risk in this prospective cohort. On the contrary, increased ATE risks have been observed with lenalidomide treatment. In the long-term follow-up of 704 patients with MM in 2 phase 3, randomized, clinical trials, the incidences of myocardial infarction and cerebrovascular events were 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone compared with 0.57% and 1.7%, respectively, in patients treated with dexamethasone alone. Therefore, lenalidomide carries a black box warning of significant myocardial
infarction and stroke risks in patients with MM receiving lenalidomide and dexamethasone treatment.\textsuperscript{15}

Thromboprophylaxis

As a result of the increasing use of IMiD-based treatment regimens, the prevention of VTEs has become an important consideration during MM treatment. Aspirin (81–325 mg daily), low-molecular-weight heparin, fixed low-dose warfarin (1–1.25 mg daily), and full-dose warfarin (target international normalized ratio, 2–3) have all been used for prophylaxis of VTEs. Fixed low-dose warfarin has generally been shown to be ineffective and is no longer used.\textsuperscript{16} Currently, there are no guidelines on the optimal thromboprophylactic regimen. The specific form of thromboprophylaxis recommended for a given patient is ultimately based on the treating physician’s best clinical judgment\textsuperscript{17} and on the patient’s individual risk factors, disease status, and treatment regimens. The International Myeloma Working Group has made an effort to create recommendations on VTE risk assessment and thromboprophylaxis. However, given the limitations of available data, these recommendations were based mainly on expert opinions; therefore, they should not be considered firm guidelines.\textsuperscript{16,17}

Table. VTE Incidences in IMiDs Trials\textsuperscript{17,25}

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>VTE Incidence Without Thromboprophylaxis, %</th>
<th>VTE Incidence With Thromboprophylaxis, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>2–10</td>
<td>NA</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>2–26</td>
<td>8–25</td>
</tr>
<tr>
<td>Plus chemotherapy†</td>
<td>3–58</td>
<td>3–31</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>0–33</td>
<td>NA</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>8–75</td>
<td>3–14</td>
</tr>
<tr>
<td>Plus chemotherapy†</td>
<td>14</td>
<td>5–9</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>NA</td>
<td>2–5</td>
</tr>
</tbody>
</table>

IMiD indicates immunomodulatory agents; and VTE, venous thromboembolic event.

*Aspirin (81–325 mg daily), low-molecular-weight heparin, fixed low-dose warfarin (1–1.25 mg daily), and full-dose warfarin (target international normalized ratio, 2–3) have all been used for prophylaxis. Choice of thromboprophylaxis was based largely on physicians’ discretion.

†Thalidomide and lenalidomide were used in combination with other therapeutic agents, including melphalan, doxorubicin, and cyclophosphamide.

Figure 3. Venous thromboembolic event (VTE) risk assessment and recommendations. Individual risk factors, myeloma-related risk factors, and therapy-related risk factors need to be evaluated carefully before the initiation of immunomodulatory drug (IMiD)–based regimens. The choice of thromboprophylactic regimen should be based on specific clinical scenarios, and this figure outlines the recommendations from the International Myeloma Working Group. The duration of prophylaxis may vary according to length of treatment. In patients with cancer, the majority of VTEs appear within 12 months from diagnosis. In MM, most VTEs have been reported in the first 6 months of treatment, and all episodes occurred within the first 12 months. Therefore, it is recommended that thromboprophylaxis be provided for the first 4 to 6 months; longer periods should be considered in the presence of additional risk factors.\textsuperscript{17} INR indicates international normalized ratio; and LMWH, low-molecular-weight heparin.
The American College of Chest Physicians guidelines recommend low-molecular-weight heparin or low-dose unfractionated heparin in outpatients with tumors and risk factors for VTEs, including thalidomide and lenalidomide therapy (Grade 2B recommendation); Figure 3).

**Questions About PIs and Risk of Thrombosis**

PIs are a cornerstone in MM management and have contributed substantially to the improvement in survival. Currently, 2 PIs, bortezomib and carfilzomib, are approved for MM treatment. Bortezomib, the first in class, was first approved in 2003, whereas carfilzomib was approved in 2012.

PIs are frequently used with IMiD-based regimens. Bortezomib, either alone or in combination, does not appear to result in an increased VTE risk, with low rates of 0% to 5%. A comprehensive review of the available data on phase 3 studies indicated that bortezomib has a protective effect against elevated VTE risk in combination with regimens of thrombogenic potential, including IMiDs. Another clinical study in which the risk of VTEs was 1.38 times higher in patients treated with thalidomide without bortezomib also suggests a possible protective role of bortezomib against VTEs.

The clinically observed thrombo-protective effect of bortezomib was supported by mechanistic studies in which bortezomib enhanced endothelial thrombomodulin expression via Krüppel-like transcription factors.

Early clinical trials with carfilzomib involved patients with MM who had been heavily pretreated and had advanced disease and in whom carfilzomib was used as single therapy. In this setting, carfilzomib, although effective for cancer therapy, showed significant cardiotoxicity. In an integrated safety analysis of all pivotal phase 2 trials in which carfilzomib was used as monotherapy in patients with MM who failed previous treatments, 22.1% had cardiotoxicity, which included cardiac arrhythmia (13.3%), heart failure (7.2%), and cardiovascular-related deaths (1.5%). Results from a recently published, randomized phase 3 trial (ASPIRE trial) comparing the efficacy of carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone showed a higher incidence of heart failure (6.4% versus 4.1%), ischemic heart disease (5.9% versus 4.6%), VTEs (10.2% versus 6.2%), and hypertension (14.3% versus 6.9%) in the carfilzomib arm. The addition of carfilzomib was more effective for MM treatment in this study, although the safety data suggested a heterogeneous pattern of cardiovascular toxicities associated with carfilzomib, with a greater presence of vascular toxicities than typical myocardial toxicity seen with other therapies such as anthracyclines. Undoubtedly, more data about the cardiovascular safety of carfilzomib, especially in the front-line setting, will emerge from upcoming studies. However, the results of ASPIRE pointed to a concerning thrombotic risk when carfilzomib is combined with lenalidomide. Cardiologists need to be aware of these toxicities and work closely with patients and their oncology teams to provide optimal cardiovascular care during MM treatment.

**Case Conclusion**

The patient was seen and followed up by a cardio-oncologist (cardiologist who focuses on cardiovascular care of cancer patients). The patient’s hypertension and diabetes mellitus increased her risk of cardiovascular toxicities, and an aggressive effort was made to control these risk factors by optimizing her hypertension and diabetes regimens. A baseline echocardiogram showed normal ejection fraction and no regional wall motion abnormalities. Laboratory results showed a creatinine clearance of 50 mL/min. Additionally, given her history of a deep vein thrombosis and other cardiovascular comorbidities, the patient was considered at high risk of developing VTEs on her combination therapy, which included carfilzomib, lenalidomide, and dexamethasone. She was prescribed enoxaparin 40 mg injected subcutaneously daily as thromboprophylaxis. She was followed up closely in the cardiology clinic, and her hypertension and diabetes mellitus were well controlled. At the 6-month follow-up, the patient had responded well to her MM therapy and had not suffered any cardiovascular events, including VTEs.

**Disclosures**

Dr Lenihan has received research funding from Takeda and has served as consultant for Onyx/Amgen. Dr Jagasia reports research funding from Therakos and Janssen. He has served as consultant for Therakos. Dr Piazza reports research funding from Bristol Myers Squibb, Daiichi Sankyo, Janssen, and the Thrombosis Research Institute. Dr Moslehi has served as a consultant for Novartis, Bristol Myers Squibb, Takeda, ARIAD, and Acceleron. The other authors report no conflicts.

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