Pulmonary Hypertension Induced by Thalidomide (and Derivatives) in Patients with Multiple Myeloma: A Systematic Review

Abdulqadir J. Nashwan1,2*, Nader I. Al-Dewik3,4,5, Hisham M. Al Sabah6, Mohamed A. Yassin6, Shehab F. Mohamed6, Nabil H. Omar7, Dana B. Mansour8

1National Center for Cancer Care & Research (NCCCR)-Hamad Medical Corporation, Doha, Qatar,
2University of Calgary, Doha, Qatar
3Qatar Medical Genetics Center, Hamad General Hospital (HGH), Hamad Medical Corporation (HMC), Doha, Qatar
4Interim Translational Research Institute (iTRI), HMC, Doha, Qatar
5Faculty of Health and Social Care Sciences, Kingston University and St George's University of London, London, United Kingdom
6Medical Oncology/Hematology Department, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar
7National Center for Cancer Care & Research (NCCCR)-Hamad Medical Corporation, Doha, Qatar
8Qatar Cancer Society, Doha, Qatar
Email: *Anashwan@hamad.qa, Naldewik@hamad.qa, Hsabah@hamad.qa, Yassin@hamad.qa, Smohamed22@hamad.qa, Namar4@hamad.qa, Dana.baseem@gmail.com

Abstract

Thalidomide is widely used in the treatment of multiple myeloma (MM). In recent years, several cases of pulmonary hypertension have been reported following treatment with thalidomide. The aim of this review was to evaluate the published literature on multiple myeloma patients with pulmonary hypertension following thalidomide treatment. A literature search was performed between 2000 and 2016. A total of 7 eligible studies were identified and deemed eligible, including 11 cases—approximately 37% (4 cases) with IgA (k), 27% (3 cases) with IgG (λ) MM, 27% (3 cases) with IgG (k) MM, and one case (9%) with primary plasma cell leukemia (PPCL). The vast majority of cases—82% (9 cases)—are associated with thalidomide, while only 18% (2 cases) are related to thalidomide derivatives (lenalidomide and pomalidomide). In conclusion, pulmonary hypertension induced by thalidomide or derivatives in multiple myeloma (MM) patients is related to a multifactorial etiology including the pathophysiology of the disease, thromboembolic events, preexistent cardiovascular conditions, comorbidities, and combination with other chemotherapeutic agents. MM patients should be evaluated for signs and symptoms underlying cardiopulmonary disease before initiating, and during treatment with thalidomide.
1. Introduction

Multiple myeloma (MM) is thrombogenic as a consequence of multiple hemostatic effects, including elevated interleukin-6 levels, procoagulant antibody formation, paraprotein interference with fibrin structure, activated protein C resistance, and endothelial damage [1] [2].

MM is a treatable, mature B-cell malignancy, which accounts for approximately 10% of the hematologic malignant neoplasms, and progress in improving survival has been rapid in recent years [3] [4] [5].

Thalidomide is active in both newly diagnosed [6] [7] [8] [9] [10] and advanced MM, and as first-line therapy in combination with dexamethasone or other cytotoxic chemotherapy [11] [12] [13]. Its mode of action includes direct apoptotic, antiangiogenic effects, and modulation of the bone-marrow microenvironment [14] [15]. However, the exact mechanism of action of thalidomide has not yet been clearly explained [16] [17].

Thalidomide has been linked with an increased risk of thromboembolic events (TEEs), including pulmonary hypertension (PH) and venous thromboembolism (VTE) [18] [19] [20]. The underlying cause of this VTE remains unclear, although several mechanisms have been postulated. It is well known that VTE can lead to PH [21].

Pulmonary hypertension is defined by a mean pulmonary artery pressure ≥25 mm Hg at rest, measured during right-side heart catheterization. The term pulmonary arterial hypertension (PAH) describes a subpopulation of patients with PH characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and a pulmonary vascular resistance >3 Wood units [22].

Pulmonary hypertension was previously classified into two categories (primary and secondary) according to the presence of identified etiology. In 1998, a clinical classification was established to personalize different classes of PH sharing similar pathological findings, hemodynamic characteristics, and management. Five groups were identified: pulmonary arterial hypertension (Group 1); PH due to left-side heart disease (Group 2); PH due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic PH (Group 4); and PH due to unclear multifactorial mechanisms (Group 5) [23].

Clinical signs include fatigue, dyspnea, dizziness, leg swelling, and chest tightness. It often progresses to right-side heart failure, which might be due to cardiac amyloidosis (CA) [24].

2. Study Objective and Significance

There has been a limited amount of research focusing on the link between thalidomide
and the development of pulmonary hypertension. The findings of this review will provide more knowledge about one of the adverse events following thalidomide treatment. The aim of this review was to evaluate the published literature on multiple myeloma patients with pulmonary hypertension following thalidomide treatment.

### 3. Materials and Methods

#### Search Strategy and Eligibility Criteria

A literature search was conducted using various databases—including PubMed, ScienceDirect, and Google Scholar—for articles published between 2000 and August 1, 2016. The following keywords: (thalidomide), (thalidomide derivatives), (lenalidomide), (pomalidomide), (pulmonary hypertension), (pulmonary arterial hypertension), and (multiple myeloma) were entered, and the search was limited to articles in English describing the association between thalidomide and thalidomide derivatives and the development of pulmonary hypertension in patients with different types of multiple myeloma. The resulting abstracts were screened, and only full-text articles published in peer-reviewed journals were retrieved for review. Reference lists were also searched to find further eligible articles. Particular attention was taken to ensure that each study was represented only once.

### 4. Results

#### 4.1. Publications Search

A total of 7 eligible studies were identified and deemed eligible: case reports (6) and a pilot study (1) published between 2003 and 2015. One study was excluded because the patient was diagnosed with Angiodysplasia, and the article was published in Spanish [25] (Table 1).

#### 4.2. Patient Characteristics

Only 11 cases of MM with pulmonary hypertension following thalidomide (and derivatives) treatment have thus far been reported: age ranges from 51 to 79 years (mean = 67.5). With regard to gender: five males (46%), 4 (36%) females, and 2 (18%) with (not available) gender. Approximately 37% (4 cases) with IgA (k), 27% (3 cases) with IgG (λ) MM, 27% (3 cases) with IgG (k) MM, and one case (9%) with primary plasma cell leukemia (PPCL). The vast majority of cases 82% (9 cases) are associated with thalidomide, while only 18% (2 cases) are related to thalidomide derivatives (lenalidomide and pomalidomide). On the other hand, the described doses varied from 50 mg/d to 400 mg/d for thalidomide. Most of the patients were presented with dyspnea, peripheral edema, and asthenia, or incidentally discovered following continual follow-up with echocardiography.

### 5. Discussion

The studies differed in several important aspects, including specific diagnosis, age...
Table 1. List of published literature on PH following treatment with Thalidomide (and derivatives).

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Diagnosis</th>
<th>Drug</th>
<th>Dose</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Presentation</th>
<th>RVSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younis, 2003</td>
<td>1</td>
<td>IgA (k), MM</td>
<td>Thal</td>
<td>400 mg/d then reduced to 100 mg/d then to 50 mg/d</td>
<td>51</td>
<td>M</td>
<td>Peripheral edema</td>
<td>70 mmHg (back to 47 mmHg after 2 months of Thal discontinuation)</td>
</tr>
<tr>
<td>Hattori et al., 2005</td>
<td>1</td>
<td>IgA (k), MM</td>
<td>Thal</td>
<td>400 mg/d</td>
<td>57</td>
<td>F</td>
<td>Mild dyspnea on exertion</td>
<td>NA</td>
</tr>
<tr>
<td>Antonioli et al., 2005</td>
<td>1</td>
<td>IgG (k), MM</td>
<td>Thal</td>
<td>100 mg/d with increase to 200 mg/d</td>
<td>63</td>
<td>M</td>
<td>Dizziness, asthenia and breathlessness</td>
<td>90 mmHg (reduced to 60 mmHg after one month of Thal discontinuation)</td>
</tr>
<tr>
<td>Lafaras et al., 2008</td>
<td>4</td>
<td>IgG (λ), MM, IgG (k), MM, IgG (k), MM, IgG (λ), MM</td>
<td>Thal</td>
<td>200 mg/d</td>
<td>59, 68, 72, 76</td>
<td>NA, NA</td>
<td>Echocardiogram</td>
<td>NA, NA</td>
</tr>
<tr>
<td>Villa et al., 2011</td>
<td>1</td>
<td>IgG (λ), MM</td>
<td>Thal</td>
<td>50 mg/d</td>
<td>79</td>
<td>F</td>
<td>Asthenia, palpitation and dyspnea on exertion</td>
<td>75 mmHg (reduced to 26 mmHg after one month of Thal discontinuation)</td>
</tr>
<tr>
<td>Tamura et al., 2014</td>
<td>1</td>
<td>Primary plasma cell leukemia (PPCL)*</td>
<td>L</td>
<td>10 mg/d</td>
<td>76</td>
<td>M</td>
<td>Leg edema and dyspnea on exertion</td>
<td>Estimated mPAP 59 mmHg</td>
</tr>
<tr>
<td>Krishnan et al., 2015</td>
<td>2</td>
<td>IgA (k) MM, IgA (k) MM</td>
<td>(L&amp;P)</td>
<td>NA</td>
<td>72, 69</td>
<td>M, F</td>
<td>Worsening dyspnea on exertion</td>
<td>83 mmHg, 65 mmHg</td>
</tr>
</tbody>
</table>

*Plasma cell leukemia (PCL), a rare but particularly aggressive form of multiple myeloma (MM), is defined by an absolute count of $2.0 \times 10^9/l$ (or 20% of peripheral white blood cell count) circulating plasma cells. [26]; NA = Not Available, Thal = Thalidomide, L = Lenalidomide, P = Pomalidomide, RVSP = Right Ventricular Systolic Pressure, mPAP = Mean Pulmonary Artery Pressure.

groups, combination protocols, duration of treatment, and the presence of comorbidities—especially thromboembolic events—which made comparisons somehow challenging.

In 2003, Younis [26] reported the first case of possible association between thalidomide and reversible PH in MM. A direct impact of thalidomide on the pulmonary vascular endothelial cells was suggested since a rapid reduction of pulmonary artery pressure after thalidomide interruption was observed.

Likewise, Hattori [27] and colleagues in 2005 also experienced the occurrence of PH in a MM patient during treatment with thalidomide by reporting the clinical course and autopsy findings. However, they clearly stated that the exact mechanism remains to be revealed; PH assessment and follow-up should be considered when thalidomide is used for MM patients. On the other hand, an autopsy revealed an extensive formation of plexogenic pulmonary arteries accompanied by the thickening of intimae and media arteries.

Six years later, Antonioli [28] and colleagues reported that one case diagnosed with II A MM IgG kappa progressed from monoclonal gammopathy of unknown significance (MGUS). The patient was refractory to different chemotherapy regimens. Later, she refused further chemotherapy and autologous transplant, which is the reason why the patient started on thalidomide, 100 mg daily, with a progressive increase to 200 mg
daily and dexamethasone for seven months without significant side effects. After one year and while on thalidomide, the patient presented to the center with dizziness, asthenia, and dyspnea. Moreover, the findings of this report supported the previous two reports in the need to clarify whether pulmonary hypertension is considered as an adverse effect of thalidomide and how the drug eventually affects the endothelial cells of blood vessels.

In 2008, Lafaras [23] and colleagues conducted the first clinical (pilot) study to detect the clinical and subclinical non-thromboembolic PH in MM patients after thalidomide treatment. The clinical and echocardiographic evaluation revealed four patients (out of 82 patients, 4.87%) with PH. Non-imaging and imaging diagnostic methods excluded thromboembolic PH. Statistical analysis demonstrated a significant correlation between structural heart disease and PH (r = 14.078; P = 0.008). No significant correlation between age, gender, International Staging System (ISS), and PH was found. Moreover, clinical assessment is essential when initially evaluating patients with suspected PH, but echocardiography is a key screening tool in the diagnostic algorithm to eliminate any secondary causes of PH, predict the prognosis, observe the efficacy of specific therapeutic interventions, and detect the preclinical stage of the disease.

In 2011, Villa [29] and colleagues reported a case of a 79-year-old woman with MM who was started on thalidomide treatment. About a month later, she presented with signs and symptoms of PH. Echocardiography revealed severe PH without cardiogenic origin, and pulmonary embolism was excluded; a previous echocardiography was normal. Thalidomide was promptly interrupted about a month later; and a physical examination and echocardiography revealed the absence of PH signs and exhibited normal parameters in both pulmonary artery pressure and right ventricular function.

In 2014, Tamura [30] and colleagues, described a case of a 76-year-old man with primary plasma cell leukemia (PPCL) complicated by renal failure and pulmonary hypertension. Bortezomib/dexamethasone (BD) induction therapy with lenalidomide was administered in association with continuous hemodiafiltration (CHDF). However, the authors described PH as a complication for the VRD protocol (bortezomib, lenalidomide, and dexamethasone), and not only the thalidomide derivative.

The most recent case report was published in 2015 by Krishnan [31] and colleagues, where three patients with MM developed severe PH. One case was excluded due to the history of cardiac amyloidosis, and no thalidomide or derivatives were initiated. In conclusion, all authors agreed that additional studies are needed to define the incidence, prevalence, prognosis, follow-up, and pathogenesis of PH in patients with different types of MM—especially for patients on thalidomide or thalidomide-derivative treatment. Further clinical trials will be needed to confirm the association between thalidomide (and derivatives) with PH in MM patients, as well as looking to the genetic predisposition for different MM mutations.

**Conflict of Interest**

The authors state that they have no conflict of interest.
Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References


the Efficacy and Safety of Single-Agent Thalidomide in Patients with Relapsed or Refractory Multiple Myeloma. *Leukemia & Lymphoma*, 48, 46-55. https://doi.org/10.1080/10428190601001904


Submit or recommend next manuscript to SCIRP and we will provide best service for you:

- Accepting pre-submission inquiries through Email, Facebook, LinkedIn, Twitter, etc.
- A wide selection of journals (inclusive of 9 subjects, more than 200 journals)
- Providing 24-hour high-quality service
- User-friendly online submission system
- Fair and swift peer-review system
- Efficient typesetting and proofreading procedure
- Display of the result of downloads and visits, as well as the number of cited articles
- Maximum dissemination of your research work

Submit your manuscript at: [http://papersubmission.scirp.org/](http://papersubmission.scirp.org/)
Or contact [jct@scirp.org](mailto:jct@scirp.org)