Background: Multiple myeloma (MM) is thrombogenic as a consequence of multiple hemostatic effects and endothelial damage. Thalidomide has been associated with an increased risk of thromboembolic pulmonary hypertension (PH). PH in the absence of venous thromboembolism has also been described in MM patients during thalidomide treatment.

Aim: Detection of clinical and subclinical nonthromboembolic PH in MM patients after thalidomide treatment.

Patients and methods: Eighty-two patients, 46–82 years (median age 61 years), 42 males, were studied. They underwent echocardiographic study at baseline, 1 month thereafter, 6 months later and whenever symptoms indicating deterioration of cardiac function appeared. Echocardiographic signs of PH were especially identified.

Results: Clinical and echocardiographic evaluation revealed four patients (out of 82 patients, 4.87%) with PH. Nonimaging and imaging diagnostic methods excluded thromboembolic PH. Statistical analysis demonstrated significant correlation between structural heart disease and PH ($r = 14.078; P = 0.008$). No significant correlation between age ($r = 0.770; P = 0.724$), gender ($r = 1.157; P = 0.285$), International Staging System (ISS) ($r = 0.316; P = 0.716$) and PH was found.

Conclusions: Preexisted endothelial dysfunction due to structural cardiac disease enhances the vasoactive substances release causing increased pulmonary vascular resistance. Thalidomide possibly causes a vasodilator and vasoconstriction imbalance, which may cause abnormal pulmonary vascular response interfering to a vicious circle perpetuating PH.

Key words: echocardiography, myeloma, pulmonary hypertension, thalidomide
patients and methods

Eighty-two newly diagnosed MM patients, 46–82 years (median age 61 years), 42 males, were studied from January 2003 to June 2007. Their evaluation was centered on the treatment plan and no prospective protocol was generated. They underwent echocardiographic study at baseline, 1 month, 6 months later and whenever symptoms indicating deterioration of cardiac function appeared. Echocardiographic signs of PH were especially identified: right atrial and ventricular enlargement, hypokinesia or hypertrophy, normal or small left ventricular dimensions, systolic flattening of intraventricular septum, as a result of the right ventricular pressure overload, pulmonary artery dilatation, pericardial effusion and septal displacement. Doppler echocardiographic quantitation of systolic arterial PH was also obtained by measuring the velocity of the tricuspid regurgitant jet using the Bernoulli formula and summing central venous pressure evaluated by inferior vena cava diameter and its alteration during inspiration as it enters right atrium from the subcostal echocardiographic view. Patients’ clinical characteristics are listed in Table 1.

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (51.2)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (48.8)</td>
</tr>
<tr>
<td>Age (median), years</td>
<td>46–82 (61)</td>
</tr>
<tr>
<td>Myeloma type</td>
<td></td>
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<tr>
<td>IgG</td>
<td>49 (59.75)</td>
</tr>
<tr>
<td>IgA</td>
<td>33 (40.25)</td>
</tr>
<tr>
<td>ISS staging system</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>23 (28.05)</td>
</tr>
<tr>
<td>Stage II</td>
<td>30 (36.58)</td>
</tr>
<tr>
<td>Stage III</td>
<td>29 (35.35)</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>26 (31.7)</td>
</tr>
<tr>
<td>Ig, immunoglobulin.</td>
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The program SPSS, version 13.0, was used for statistical analysis. Multinomial regression stepwise analysis was used to study the correlation of age, gender, preexisting structural heart disease and ISS with PH.

results

Clinical and echocardiographic evaluation revealed four (out of 82, 4.87%) patients with PH. They were all newly diagnosed MM patients and treated with thalidomide, 200 mg daily plus dexamethasone and low-molecular weight heparin (LMWH) as thromboprophylaxis. Amyloidosis was ruled out in all four patients by abdominal fat pad fine-needle aspiration biopsy.

One patient had clinical symptoms and signs of right heart failure 3 months after thalidomide administration with progressive deterioration. He was a 59-year-old man with MM IgG, λ light chains and extensive diffuse bone marrow infiltration (85% infiltration). Echocardiogram carried out at baseline revealed mild aortic regurgitation due to mild calcification of noncoronary cusp, good biventricular function, mild left ventricular hypertrophy diastolic dysfunction of impaired relaxation, no evidence of PH and no signs of amyloid cardiac infiltration. He had no history of obstructive pulmonary disease and his functional status was class I New York Heart Association.

Echocardiographic evaluation 3 months later confirmed the clinical signs of right heart failure and PH: good left ventricular size and function, right atrial and ventricular dilatation, moderate tricuspid regurgitation due to tricuspid ring dilatation, with estimated right ventricular systolic pressure of 98 mmHg and a systolic pulmonary artery pressure of 104 mmHg. Vein ultrasonography failed to establish the presence of deep venous thrombosis. As lung perfusion scintigraphy was negative for pulmonary embolism, thromboembolic PH was excluded. The second bone marrow histology confirmed therapeutic response to thalidomide. Thalidomide was discontinued and the patient was treated with diltiazem, Angiotensin-Converting Enzyme, inhibitor, furosemide and bosentan (62.5 mg b.i.d. for 1 month and 125 mg b.i.d. thereafter). It is noted that pulmonary pressure value, while improving, did not recover up to the baseline value, possibly because of an irreversible drug effect on endothelial and muscle vessel cells.
The second patient was a 68-year-old woman with IgG, κ light chains MM. Echocardiogram at baseline identified good biventricular systolic function and left ventricular diastolic dysfunction of impaired relaxation. Echocardiographic study 6 months after thalidomide administration detected mild PH (54 mmHg) without clinical symptoms of functional status deterioration. Her medical history was unremarkable except for arterial hypertension. The other two patients (72 and 76 years, with IgG, κ light chains, and IgA, λ light chains, respectively) had coronary artery disease and developed subclinical PH, 1 and 3 months after thalidomide administration. Diltiazem (one patient), amlodipine (two patients) and furosemide were administered to all three patients without discontinuation of thalidomide. Nonimaging (plasma D-dimers and electrocardiogram) and imaging (chest roentgenography, lung scanning and chest computed tomography) diagnostic methods excluded thromboembolic PH.

Treatment of PH included lifestyle modifications, conventional treatment with calcium channel blockers and diuretics and specific treatment with the endothelin antagonist bosentan (one patient). Response to therapeutic interventions was evaluated clinically (symptoms and exercise tolerance) and confirmed by echocardiography.

Statistically significant correlation between age (r = 0.770; P = 0.724) and PH development, as well as gender (r = 1.157; P = 0.285), ISS staging (r = 0.316; P = 0.716) and PH, was not found. On the contrary, a significant correlation between structural heart disease and PH was observed (r = 14.078; P = 0.008) (Figure 1). Our results indicate that the subgroup of MM patients with known heart disease (coronary artery disease, valvular heart disease and hypertension) receiving thalidomide should be thoroughly examined by echocardiography for the early detection of clinical and/or subclinical PH.

discussion

Thalidomide was initially used in MM, because of its antiangiogenic activity, given that increased angiogenesis occurs in the bone marrow of MM patients [26, 27]. Singhal et al. [28] reported that thalidomide had activity in MM with a 32% response rate when used as a single agent in relapsed disease. Nevertheless, it was soon discovered that thalidomide has additional mechanisms of action [29]. Subsequent studies have demonstrated a synergistic effect with other agents and thalidomide is now widely used at all stages for myeloma therapy [30]. Despite clinical activity, it remains uncertain as to exactly how these effects are mediated. Thalidomide certainly has promiscuous actions with antiangiogenic activity, direct antimyeloma effects and immunomodulatory properties [19, 31]. The relative importance of these individual activities, however, has to be determined.

Vascular involvement seems to be a plausible mechanism in the pathophysiology of PH. Thrombosis is observed frequently in the small vessels of patients with PH and is thought to be a consequence of platelet activation at the site of endothelial injury and low rates of flow through the altered vessels [31]. On the other hand, preexisting endothelial dysfunction due to structural cardiac disease enhances the vasoactive substances release causing increased pulmonary vascular resistance [32, 33].

It is common knowledge that the vascular endothelium plays a central role as a mediator of pulmonary vasoconstriction through balanced release of nitric oxide (NO) and endothelin particularly in small pulmonary arteries and arterioles [33, 34].

Figure 1. Significant correlation between structural heart disease and PH (r = 14.078; P = 0.008). CAD, coronary artery disease; VD, valvular disease. Column A: Patients without structural heart disease. Column B: Patients with CAD. Column C: Patients with hypertension. Column D: Patients with mitral valvular disease. Column E: Patients with aortic valvular disease.
NO inhibits the growth of vascular smooth muscle cells and is probably involved in vascular remodeling in response to injury and is also important in the signal transduction of angiogenesis [35, 36]. As understanding of vascular biology improves, abnormalities in pulmonary endothelial cell function are essential as causing or contributing to the development of PH. Dysfunction of the counter-regulatory systems within the pulmonary vascular bed seems to be common causing increased pulmonary vascular reactivity, vasoconstriction and inappropriate smooth muscle hypertrophy. Although it is unsettled whether reduced NO synthase production is a cause or a result of the disease, it is consistent with endothelial dysfunction underlying PH as part of the disease process.

Endothelin may also play an important role in the elevated pulmonary vascular tone. Additionally, high pulmonary blood flow, caused by MM, may have effects on pulmonary endothelium through some type of mechanical means that would cause perturbations in the integrity of vascular wall. A prothrombotic state can arise as a consequence of fibrinolysis, enhanced coagulation or increased platelet activation which not only promotes thrombosis but also leads to the release of granules that contain mitogenic agents and vasoconstrictive substances and leads to the development of PH. Thalidomide possibly causes a vasodilator and vasoconstriction imbalance which may cause abnormal pulmonary vascular response interfering to a vicious circle perpetuating PH [37–39].

In an effort to improve the toxicity profile of thalidomide (neuropathy, constipation and TEEs), while maintaining the efficacy of the drug, the immunomodulatory derivative (IMiD) lenalidomide was developed. Lenalidomide, a structural analog of thalidomide, is in vitro a 200–50 000 times more potent immunomodulator than thalidomide and appears to be the most promising of the second-generation IMiDs agent in phase II, phase III and international studies alone and in combination with dexamethasone, respectively, in relapsed and refractory disease [30, 40]. In the new era of lenalidomide, the possibility of PH development should be noted and the close echocardiographic monitoring of myeloma patients receiving this drug may be of great value.

Both agents appear to increase the risk of TEEs, although the actual baseline incidence is unclear [40]. The TEEs incidence in newly diagnosed myeloma patients receiving thalidomide plus dexamethasone without thrombosis prophylaxis is ~15% [28]. An 8.5% incidence of TEEs in patients with relapsed or refractory disease getting lenalidomide plus dexamethasone without prophylaxis has been reported [40]. It is important to notice that in all patients of our study who developed PH, it was excluded to be secondary to thromboembolic disease, according to imaging and nonimaging techniques. Additionally, these patients were receiving thromboprophylaxis with LMWH.

PH can be catastrophic and myeloma is a predisposing condition with therapeutic implications that can increase its incidence. Thus, monitoring is likely to be of value because early identification may allow intervention and thus improve quality of life and survival. Modern therapeutic intervention of PH includes the dual endothelin A/B receptor antagonist bosentan and two selective endothelin A receptor antagonists, sitaxsentan and ambrisentan. Phosphodiesterase-5 inhibitors (sildenafil and tadalafil) have also been evaluated for the treatment of PH. Combination therapy is promising for inducing the most complete vascular remodeling of the pulmonary vasculature by ‘shutting down’ the multiple pathways promoting PH [41, 42].

Moreover, various novel approaches of antimyeloma therapeutics have become available. Defibrotide (DF), a polydisperse mixture of single-stranded oligonucleotide with antithrombotic and fibrinolytic effects on microvascular endothelium, has emerged as an effective and safe therapy used in the treatment of endothelial complications in the course of allogeneic stem cell transplantation. Recent preclinical evidence indicates that DF might also have antineoplastic properties inhibiting tumors, via an antiangiogenic effect [43]. The interesting work led by Palumbo et al. [44] on the combination of DF with melphalan, prednisone and thalidomide in myeloma to reduce thromboembolic complications as well as targeting endothelial cell injury is promising, both in terms of specifically targeting the tumor microenvironment and low rate of TEEs.

Nonthromboembolic PH is not rare in MM patients and echocardiographic evaluation might be necessary to all patients receiving thalidomide or IMiDs. Although clinical assessment is essential when initially evaluating patients with suspected PH, echocardiography is a key screening tool in the diagnostic algorithm. It not only provides an estimate of pulmonary pressure at rest and during exercise but also may help to exclude any secondary causes of PH, predict the prognosis, monitor the efficacy of specific therapeutic interventions and detect the preclinical stage of the disease.

references


