

Thalidomide-associated Arterial Thrombosis: Two Case Reports

Introduction

Thalidomide was used as a sedative in the 1950s and was withdrawn from the market after initial reports of teratogenicity in 1961. In 1998, the US Food and Drug Administration (FDA) approved the drug as a treatment for erythema nodosum leprosum. The finding of increased angiogenesis in myeloma, coupled with the recognition of the antiangiogenic properties of thalidomide, led to the first clinical trial of this drug for the treatment of multiple myeloma (MM) at the University of Arkansas.¹ Besides teratogenicity, other important toxicities are peripheral neuropathy, rash, sedation, constipation, fatigue, pruritis, and hypothyroidism. With the increasing use of thalidomide as initial therapy for MM, deep venous thrombosis (DVT) and other thrombotic events have also emerged as major adverse events.^{2,3} The incidence of DVT is only 1% to 3% in patients receiving the drug in combination with dexamethasone and about 25% in patients receiving the drug in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin.¹ While there are several reports of venous thrombotic events related to thalidomide use, there are few reports pertaining to the arterial thrombotic events during thalidomide therapy.^{2,3}

We herein describe 2 patients complicated by an arterial thrombosis induced by thalidomide therapy which was administered for MM. The absence of history of thrombosis prior to thalidomide therapy, the intensity of thrombotic event, and the short interval between initiation of thalidomide and the occurrence of arterial vascular event were remarkable. In this report, we have noted the risk of arterial thrombosis during thalidomide therapy.

Case Reports

Case 1

A 48-year-old male patient with MM received 5 cycles of vincristine, adriablastina, dexamethasone (VAD) protocol. Due to the patient's disapproval of high-dose chemotherapy plus stem cell transplantation, thalidomide therapy at a dose of 200 mg/day was initiated. The pulse pattern before acute episode by clinical examination was normal. On the 28th day of therapy he had pain and numbness in the left leg, followed by bruising. Lower extremity arterial doppler ultrasonography revealed 20% to 50% occlusion in the left femoral artery. Thrombus in the left iliac and femoral artery and occlusion in the left popliteal artery were detected by angiographic examination. Echocardiography was normal.

Hereditary causes of thrombophilia including factor V Leiden, prothrombin gene mutations, antithrombin III, protein C and protein S deficiencies were not found. Diabetes mellitus (DM) and hyperlipidaemia were not detected. There is no family history of atherosclerosis. Thalidomide therapy subsequently discontinued, anticoagulant therapy and low-dose aspirin was initiated. Left femoral embolectomy was performed and pulsation on the popliteal artery were recovered. Warfarin and low-dose aspirin therapy still remains after the thromboembolic event.

Case 2

Thalidomide at a dose of 100 mg/day plus dexamethasone therapy was administered to a 60-year-old male patient with MM. In the subsequent week after the initiation of therapy, the dose of thalidomide was increased to 200 mg/day. Clinical examination of the pulse pattern before the acute episode was normal. On the 15th day of therapy, he had pain, numbness, paleness and coldness on the left leg. Pulsation on the artery of dorsalis pedis could not be perceived and the left thumb was gangrenous. Arterial doppler ultrasonography indicated more than 50% occlusion in the posterior tibialis and peroneal artery. Left popliteal artery occlusion was detected by angiographic examination. Echocardiography was normal. The patient had a 10 pack year smoking history and quit 17 years prior to the thrombotic event. Hereditary causes of thrombophilia were excluded. Other thromboembolic predispositions such as DM or hyperlipidaemia were also not observed in the patient. Thalidomide therapy was withdrawn and embolectomy was performed. Oral anticoagulant and low-dose aspirin therapy was still continued.

Discussion

Malignancy is a well known acquired thrombophilic condition and several types of hamostatic system abnormalities are related to solid tumours and leukaemias.⁴ Multiple factors may contribute to generate a hypercoagulable state in cancer patients, including procoagulants produced by tumours, vascular invasion, elevated level of factors V, VIII, IX and XI, decreased levels of protein C, antithrombin, physical inactivity, indwelling venous devices, chemotherapy-induced changes, inherited or acquired thrombotic tendencies. Age and smoking are also risk factors for thrombosis.⁵

The pathogenesis of thalidomide-induced thrombosis is

poorly recognised and has been described in malignant and non-malignant states.⁶ The risk of venous thromboembolism on thalidomide therapy has been well-documented, but there are few reports mentioning arterial thrombotic events during thalidomide therapy.⁷ Although single-agent thalidomide has minimal prothrombotic activity, the risk of thrombosis increases significantly when combined with cytotoxic chemotherapy.⁸ Among patients treated with thalidomide and dexamethasone, 3.4% to 7% experienced a thrombotic event, but the incidence increased up to 25% when thalidomide was combined with anthracycline-containing chemotherapeutic regimens.^{1,4,9}

The development of DVT early in the course of therapy, within the first 60 days, suggests that this complication may be related to the release of thrombotic factors from apoptotic myeloma cells rather than cumulative thalidomide exposure.⁸

MM patients do not show increased thromboembolic predisposition when compared with other malignancies. Other underlying causes of thrombosis include von Willebrand factor levels, von Willebrand factor antigen and pro-coagulant factor VIII level, anti-thrombin III deficiency, protein C deficiency and protein S deficiency. Lupus anticoagulant, antiphospholipid antibodies and prothrombin gene abnormalities are not responsible for thrombosis in MM patients.⁷ Explanations for the high rates of thalidomide-related thromboembolic events are apoptosis of tumour cells induced *in vitro*, increased activation of tissue factor in the plasma membrane of tumour cells, alteration of tumour cell interactions with coagulation factors, activating platelets or vascular endothelium, impairment of endothelial cell function by free radical-mediated oxidative deoxyribonucleic acid damage and induction of a Th-1 cellular response leading to increased secretion of interferon γ and interleukin 2. Interferon γ increases the thrombogenicity of endothelial cells. The combination of chemotherapy-induced endothelial cell damage and thalidomide-induced increments in integrin levels can lead to tumour cell adhesions and platelet clumps, which can be thrombotic.¹⁰ Zangari et al reported that risk factors for DVT in MM included acquired activated protein C resistance, previously untreated newly diagnosed disease, chromosome 11 abnormalities and age more than 60 years.^{3,11}

In our clinic, thalidomide was administered to 13 patients with MM. Two of the 13 patients had arterial thrombosis and venous thromboembolism was detected in another 2 patients. None of these 4 patients had predisposing factors for thrombosis, such as hereditary thrombophilia and lupus anticoagulant, but the 2 patients with arterial thrombosis were male and older than 45 years of age. Prothrombotic predisposition was not present in 2 patients with arterial

thrombosis when compared to the other 9 patients without thrombotic event. But our second patient with arterial thrombosis was 60 years old and was on an initial therapy of thalidomide and dexamethasone. High total tumour burden may play a role in the pathogenesis of thrombosis in this newly diagnosed patient. Thalidomide therapy was initiated subsequent to 4–5 cycles of VAD protocol, which lead to relatively low tumour burden in the remaining patients. The short interval between thrombotic events and the initiation of thalidomide therapy, and the absence of any other remarkable thrombotic risk factors suggest that thalidomide the agent responsible for arterial thrombosis. Although there is no established prophylactic therapy for thrombotic events of MM patients during thalidomide administration, some reports point out that oral anticoagulation is beneficial but not satisfactory and low-dose aspirin may decrease the frequency of thrombotic events.^{11,12} Once thrombosis has occurred, patients must be treated with standard anticoagulation with heparin or with low-molecular-weight heparin followed by warfarin. Thalidomide can be resumed safely after adequate anticoagulation, and anticoagulant therapy is administered until at least as long as therapy with thalidomide is continued.¹¹

Conclusion

Thromboembolism may occur early after the initiation of thalidomide therapy even with low-dose treatment. Lower extremity DVT is the most frequent type of thrombotic complication seen with thalidomide therapy. Physicians should be aware of the risk of thalidomide-related arterial thrombosis. Although efficacy of prophylactic anticoagulation on thalidomide therapy was not ascertained, the authors suggest that anticoagulant therapy should be administered during thalidomide treatment because of higher frequency of thalidomide-related arterial and venous thrombosis.

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