Thalidomide and Thrombosis

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Thalidomide is a glutamic acid derivative that exerts potent anti-angiogenic activity, modulation of T-cell activity and direct effects on tumour cells and their microenvironment. For its anti-inflammatory activity, mainly due to inhibition of TNF- α production, this agent is used to treat leprosy (registered use), lupus erythematosus, atopic dermatitis and Behçet's disease. The anti-angiogenic activity of thalidomide suggested its use for the treatment of both solid and hematologic malignancies. Elevated levels of proangiogenic factors, particularly vascular endothelial growth factor (VEGF) have been associated with a poor prognosis in leukemias, multiple myeloma and NHL. In addition, a direct relationship between VEGF production and leukemic blasts and malignant plasma cells proliferation has been established, thus anti-VEGF agents are being evaluated in many protocols. The anti-angiogenic activity of the drug may be due to a reduction of both VEGF and b-FGF (basic fibroblast growth factor) levels, although discordant findings have been reported [1]. Thalidomide was shown to be effective in relapsed or refractory multiple myeloma and its role as part of the initial treatment armamentarium is under investigation. The anti-myeloma effect is mediated by several mechanisms: induction of G1 growth arrest/apoptosis by inhibiting NF- κ B and activating caspase 8; inhibition of adhesion of myeloma cells to bone marrow stromal cells; inhibition of secretion of cytokines (TNF- α , IL-6, IL-1 β); induction of T cell and NK cell anti-myeloma immunity and inhibition of angiogenesis.

Incidence of Thalidomide-Associated Thrombosis

Among thalidomide-related side effects, teratogenic activity and neuropathy were considered as the most serious adverse effect when the drug was used in a variety of non-malignant conditions, although severe thrombotic events have been occasionally reported also in patients with lupus erythematosus or aphtosis. Notably, thrombosis was not observed when thalidomide was used in pregnant women during the '50s. However, from the experience with myeloma patients, venous thromboembolism (VTE) has recently emerged as the single most important complication. An increased incidence of venous thromboembolism was observed also in other malignancies during treatment with thalidomide combined with chemotherapy. Incidence rates reported in different studies were 7% for myelodysplastic syndromes treated with thalidomide alone [2]; 9/100 patient-years in an ongoing protocol for myelofibrosis (M. Marchetti, personal communication); 19% in patients with metastatic prostate cancer treated with thalidomide associated with docetaxel [3] and 43% in patients with metastatic renal cancer when thalidomide was combined with gemcitabine and fluorouracil [4]. Most data regarding the association of thrombosis with thalidomide come from studies in multiple myeloma patients, where this drug finds its main application.

Table 1. Incidence of venous thromboembolism

Regimen	Incidence of VTE (%)	Patients	Reference
Thal 200–800 mg/die	<2	169 advanced and refractory	Barlogie et al., 2001
Thal alone	4.6	326	Bennett et al., 2001
Thal 200–800 mg/die	4	25 relapsed	Helgi et al., 2002
Thal 200–600 mg/die	3	28 newly diagnosed	Weber et al., 2002
Thal 200–800 mg/die	3.4	31 with smouldering or indolent MM	Rajkumar et al., 2002
Thal 100–800 mg/die	1.5	65 relapsed and refractory	Tosi et al., 2002
Thal 200–600 mg	3	28 newly diagnosed	Weber et al., 2002
Thal 100–400 + dexamethasone	25 (warfarin 1 mg/die) 7 (INR 2–3)	70 newly diagnosed	Weber et al., 2002
Thal 100–200 mg/die + CHT	27.8	18 relapsed or refractory	Camba et al., 2001
Thal 100–200 mg/die + dexamethasone	26	19 newly diagnosed	Cavo et al., 2002
Thal 200 mg + dexamethasone	12	50 newly diagnosed	Rajkumar et al., 2002
Thal 100–300 mg/die + DCEP	21	14 advanced refractory	Urbauer et al., 2002
Thal 400 mg + CED	4.2	95 refractory	Moehler et al., 2002
Thal 100–200 mg + doxo and dexamethasone	27	15 newly diagnosed	Osman et al., 2001
Thal 400 mg + Total therapy	28	100 newly diagnosed	Zangari et al., 2001
DT-PACE (Thal 400 mg)	16	192 relapsed after conventional treatment	Zangari et al., 2002
Thal 400 mg + DCEP	2.5	40 relapsed after high-dose therapy	Zangari et al., 2002
Thal + melphalan and prednisolone	23	newly diagnosed	Oakervie et al., 2002
	11	advanced	

Thal – Thalidomide; CHT – chemotherapy; DCEP – dexamethasone, cyclophosphamide, etoposide, cisplatin; CED – cyclophosphamide, etoposide, dexamethasone; doxo – doxorubicin; DT-PACE – dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide.

Hypercoagulability has been observed in patients with multiple myeloma and has been associated with deep-venous thrombosis (DVT) in 10% of treated patients [5]. When thalidomide was used as single agent, the incidence of VTE was <5% in many studies (see table 1), but the incidence rate increased when thalidomide was used in combination with chemotherapy, especially doxorubicin-containing regimens. In an analysis of data obtained from MedWatch, the FDA's passive reporting system, the incidence of thromboembolic events in cancer clinical studies was 4.6% among patients treated with thalidomide alone, 15.0% among patients who also received dexamethasone and 30.9% among patients who received thalidomide plus chemotherapy [6]. In the Total Therapy II phase II study, 100 newly diagnosed patients were randomly assigned to receive identical induction chemotherapy with or without thalidomide: DVT developed in 28% of patients receiving thalidomide (400 mg daily) but only in 4% of the control arm ($P = 0.002$); one episode of pulmonary embolism was reported in the thalidomide arm [7]. All events of VTE occurred during the first 3 cycles of therapy (VAD followed by DCEP and by cyclophosphamide, doxorubicin and dexamethasone). Baseline plasma risk factors (protein C and S activity, antiphospholipid antibodies and activated protein C resistance) were not significantly different in the two groups. However, the patients in the thalidomide arm

had less antithrombin activity, lower fibrinogen levels and a higher proportion of von Willebrand factor antigen. All patients had central venous catheters (CVC). Thrombosis was related to CVC in only 3/14 VTE episodes in patients treated with thalidomide compared with 1/2 in the control arm, thus the increase in risk is higher for distant, non-CVC-related sites. Administration of thalidomide was resumed in most patients (75%) after successful anticoagulation therapy. Urbauer et al. [8] confirmed the observation of increased incidence of VTE in this setting, reporting a 21% rate of thromboembolic events in 14 refractory patients receiving DCEP combined with thalidomide, that was continued as maintenance therapy. However, 2/3 deep-vein thrombosis developed late, during the maintenance therapy. In contrast with these data, Moehler et al. [9] observed a low incidence of VTE when thalidomide was included in a combination regimen without doxorubicin. 95 refractory patients were treated with thalidomide (400 mg daily), cyclophosphamide, etoposide and dexamethasone and only 4 patients (4.2%) developed thrombotic events. In order to assess the role of doxorubicin, Zangari et al. [10] analysed the incidence of VTE in two groups of patients treated with combinations of thalidomide and chemotherapy that differed only by the inclusion of doxorubicin in one protocol: VTE was observed in 16% of patients who received doxorubicin-containing regimen compared with

2.5% in the control arm ($P = 0.02$). Overall, 69% of the thromboembolic events occurred within the first 60 days of therapy. Time to VTE was shorter for the patients exposed to doxorubicin.

The combination of thalidomide and chemotherapy produced an higher risk of VTE when it was administered to newly diagnosed patients rather than to relapsed or refractory patients. Rajkumar et al. [11] reported a 12% incidence of VTE using thalidomide combined with dexamethasone as initial therapy. In this setting Cavo et al. [12] observed a 26% incidence of VTE, which was higher than that observed when the same regimen was used in relapsed or refractory patients. Similarly, Osman et al. [13] reported an excessive rate of VTE by using thalidomide, doxorubicin and dexamethasone in previously untreated patients: 4/15 (27%) developed thrombosis and the trial was therefore suspended. In addition, the major risk of thrombosis occurs early after initiation of the treatment, when the tumour load is maximal. Thus, this complication may be related to the release of thrombogenic factors from myeloma cells rather than to the cumulative drug exposure. In this regard, table 1 shows no clear correlation between DVT and the dose of thalidomide administered. However, the study of Zangari et al. [10] failed to show a significant association between DVT and response $>50\%$ to the therapy. In the UKMF T-VAD protocol, thalidomide was added to chemotherapy only after an initial VAD course and cyclophosphamide administration, resulting in a tumour reduction prior to T-VAD [14]. Of the first 12 patients enrolled, only 1 (8.3%) has developed a thromboembolic event [15]. In our center, 58 relapsed or refractory patients were treated with thalidomide: we observed 8 cases of VTE, with an incidence of 0.19/patient-years (0.08–0.37 95% CI), with no correlation with age, sex, or concomitant use of dexamethasone or chemotherapy.

Suggested Pathogenetic Mechanisms

Overall, the combination of thalidomide, chemotherapy (especially doxorubicin containing regimens) and large tumour burden results in an increased risk of thromboembolic events in multiple myeloma. The pathogenesis of this prothrombotic state has not yet been established. The thrombotic events occurred mainly within a brief delay after the onset of thalidomide, which seems therefore to play a role as a precipitating or starting factor. Many other risk factors are present in myeloma patients, such as age, increased plasma viscosity, immobility, performance status, presence of a CVC and concomitant infections.

The role of certain serum hypercoagulable features is under investigation. Zangari et al. [16] tested for hypercoagulability 62 newly diagnosed patients at baseline, who were subsequently randomised to receive chemotherapy with or without thalidomide. The two study arms were comparable for baseline myeloma prognostic factors and known conventional risk factors for DVT. 23% of the patients had APC resistance in absence of factor V Leiden mutations, with no significant difference between the two arms; none showed prothrombin gene abnormality. 12 patients (19% of the entire group) developed DVT, 11 in the thalidomide arm and only 1 in the control group ($P = 0.001$). DVT was more frequent in those patients with acquired APC resistance (36% vs. 15%, $P = 0.04$). Thus, the risk of DVT was highest in patients with APC resistance treated with thalidomide combined with chemotherapy (incidence 50%). Protein S deficiency or elevated factor VIII has been observed in one-quarter of the patients with APC resistance. It is not yet clear whether APC resistance disappears with an effective anti-myeloma therapy. In patients with multiple myeloma, the plasma concentration of factor VIII and von Willebrand factor antigen (VWF:Ag) are frequently increased; in addition, VEGF levels increase with progression of the disease, especially after the use of thalidomide. Ward et al. [17] studied factor VIII coagulant activity (FVIII:C), VWF:Ag and acquired resistance to activated protein C during the treatment with thalidomide for malignancies; many patients who developed thrombosis had pre-existing elevated coagulation factors or APC resistance; patients with baseline normal coagulation parameters showed an increase of FVIII:C and VWF levels while on thalidomide. However, the role of VEGF, FVIII:C and VWF in the pathogenesis of DVT in myeloma patients treated with thalidomide still remains unclear [18]. Weber et al. [19] evaluated prothrombotic factors prior and after treatment including thalidomide: 56% of the patients had elevated homocystein levels, 42% low AT, 49% MTHFR gene mutations, 18% low protein C, 12% low protein S, 8% lupus anticoagulant. Re-evaluation after treatment showed normalisation of AT deficiency and no consistent effect on the other factors.

To explain the increased risk of thrombosis in patients receiving thalidomide combined with chemotherapy, Kaushal et al. [20] hypothesized an effect of thalidomide on the endothelium. In a experimental model, the addition of thalidomide to uninjured arterial endothelium did not cause any appreciable change, whereas thalidomide added to adriamycin-injured (8–24 h) endothelial cells resulted in cell detachment and formation of apoptotic vesicles. An increase of tissue factor levels and upregulation of protease-activated receptor-1 were also observed. More recently, the

same group showed an increased caspase-3 activity after incubation of cultured endothelial cells with doxorubicin, whereas incubation with thalidomide resulted in decreased caspase-3 activity. In addition, when cells previously exposed to doxorubicin were incubated with thalidomide, there was marked formation of neotubules and proangiogenesis through stimulation of thrombin receptor [21]. The procoagulant and proangiogenic activities of thalidomide in doxorubicin-injured endothelium, suggested by these findings, requires further investigations in in vivo models. An interesting prospective is the possibility to separate the anti-tumor from the procoagulant activity of thalidomide. Using the immunomodulatory derivatives

(IMiDs) of thalidomide it was not observed until now any association with an increased risk of thrombosis, while maintaining or increasing the anti-myeloma efficacy. Many pathogenetic mechanisms are probably still unknown and prospective studies with large population are required to better define the groups of patients with the major risk of VTE.

It remains also to be assessed what is the most effective method of VTE prophylaxis: therapeutical doses of warfarin (INR between 2 and 3) or prophylactic low molecular weight heparin are effective options to prevent thrombosis, whereas low dose of warfarin (1mg daily) failed to decrease significantly the thrombotic complications [22].

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