Efficacy and Safety of Danshen Compound Tablets in Preventing Thalidomide-Associated Thromboembolism in Patients with Multiple Myeloma: A Multicenter Retrospective Study

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Background: Currently available antithrombotic prophylaxis is not perfectly reliable in elderly patients. The aim of this retrospective study was to evaluate the efficacy and safety of Compound Danshen Tablet (CDT) in preventing thromboembolism in multiple myeloma (MM) patients treated with thalidomide-based regimens.

Material/Methods: MM patients treated with thalidomide-based regimens were retrospectively reviewed between January 2008 and March 2015. Patients were categorized into 3 cohorts based on thromboembolic prophylaxis used: CDT, Warfarin Tablet, and no prophylaxis. Venous thromboembolism (VTE), other adverse effects (AEs), and the changes of D-dimer and fibrinogen levels were monitored.

Results: Seven out of 313 MM patients (2.24%) developed venous thrombosis events (VTE) in this retrospective study, all clustering in the no prophylaxis cohort. Three patients of the Warfarin cohort (3.19%) experienced hemorrhage. Neither VTE events nor serious AEs were observed in the CDT cohort. Following Compound Danshen or Warfarin treatment for 3 months, the D-dimer and fibrinogen levels (in particular the D-dimer level) (all $P<0.05$), were obviously decreased relative to their respective baselines and the no prophylaxis cohort. In contrast, the 2 blotting parameters were significantly increased in the no prophylaxis cohort relative to the baseline level (All $P<0.05$), and were even higher in the patients experiencing VTE compared to the no VTE patients ($P<0.0001$ and $P=0.016$, respectively).

Conclusions: Our findings indicate CDT is an effective therapy for preventing VTE in MM patients treated with thalidomide-based regimens, and is well tolerated in long-term use.

MeSH Keywords: Multiple Myeloma • Thalidomide • Venous Thrombosis

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Background

Multiple myeloma (MM) is a plasma cell neoplasm character-
ized by the presence of monoclonal immunoglobulin in the
serum and/or urine and clinical symptoms related to end-or-
gan damage comprising hypercalcemia, renal insufficiency,
anemia, and bone complications (CRAB features) [1]. MM ac-
counts for approximately 1% of all types of cancer and 13%
of hematologic malignancies, and primarily affects the elder-
ly, with a median age at diagnosis of about 70 years [2]. The
prognosis of MM is heterogeneous due to patient-related risk
factors such as age and comorbidity, as well as disease- related
risk factors such as stage and cytogenetic abnormality [1]. In
the last decade, the outcome of MM patients has been signif-
icantly improved since the introduction of bortezomib, a pro-
teasome inhibitor, and the immunomodulatory drugs (IMiDs)
lenalidomide and thalidomide [3]. These drugs have large-
ly improved the rate of complete remission, and significantly
increased the time to progression, progression-free survival,
and overall survival [4,5].

Of these new agents, thalidomide has been the most wide-
ly used drug for the treatment of MM due to its low cost and
easy availability. However, it has been reported that the use
of thalidomide alone has been linked to an increase in the in-
cidence of VTE by at least 2.1-fold. VTEs increased up to 3.1
times, when thalidomide is administered in combination with
high-dose dexamethasone [6]. Incidences of VTE were more
frequent during the first 3–6 months of thalidomide treat-
ment [7,8]. Thus, the use of thalidomide-containing regimens
should be carefully monitored to prevent thrombosis events [9].

To date, the clinical benefits of single-agent antithrombot-
ic prophylaxis have been reported [10,11]. Although aspirin,
warfarin, and low-molecular-weight heparin are all acceptable
strategies for antithrombotic prophylaxis, none of them is per-
fectly reliable. As the primary severe adverse effect (SAE) of
anti-thromboembolism is bleeding, and other adverse effects
include stomach pain or headache pain, dizziness, and weak-
ness, safety should be addressed for long-term use in MM pa-
tients, particularly in elderly patients undergoing chemother-
apy [10,11]. Compound Danshen Tablet (CDT), a traditional
Chinese herbal preparation, consists of *Salvia miltiorrhiza* (ra-
dix and rhizome of *Salvia miltiorrhiza* Bge.), accounting for 75%
of total phytochemicals, Notoginseng (radix and rhizome of
Panax notoginseng) accounting for 24% of chemical constit-
uents, and *Borneolum syntheticum* (1% of chemical constitu-
ents) [12]. CDT has many pharmacological effects, including
dilation of coronary arteries, decrease of myocardial oxygen
consumption, and improvement of blood viscosity and micro-
circulation, thus it is widely used to treat cardiovascular dis-
orders [13], atherosclerosis [14], unstable angina pectoris [15],
diabetes [16], and diabetic retinopathy [17].

Although many pharmacological activities of CDT have been
determined, little is known about its anti-thromboembolic ef-
fect in MM patients. In this retrospective study, we evaluated
the efficacy and safety of CDT for thromboembolism preven-
tion in MM patients treated with thalidomide-based regimens,
based on the patients' clinical outcomes and the changed
D-dimer and fibrinogen levels.

Material and Methods

Study population and data collection

We retrospectively reviewed all of the patients diagnosed with
MM and treated with thalidomide-based chemotherapy from
January 2008 to March 2015 in the Affiliated Cancer Hospital
of Zhengzhou University, The Central Hospital of Xinxiang, and
The Second People's Hospital of Jiaozuo. Patients were exclud-
ed from the current retrospective study if they had a history
of VTE or existing VTE before treatment, erythropoietin-stim-
ulating factor treatment, less than 2 months of anti-thrombo-
embolism therapy, other malignancies, or blood clotting disor-
ders. Clotting parameters, such as prothrombin time, activated
partial thromboplastin time, international normalization ratio,
D-dimer, fibrinogen, and whole blood counts, were analyzed.
Information regarding the incidence of thrombosis and oth-
er AEs was carefully collected in each cohort from initiation
of anti-thromboembolism therapy to discontinuation of anti-
thromboembolism therapy and chemotherapy. The study pro-
tocol for the collection of clinical information was approved
by Henan Cancer Hospital Review Board and was conducted
according to the Helsinki Declaration.

Administration of thalidomide and anti-thromboembolism therapy

Thalidomide-based chemotherapy regimens consisted of thalid-
omide (100–200 mg, once before sleep every night) (Changzhou
Pharmaceutical Factory, Changzhou, Jiangsu, China) in combi-
nation with other chemotherapy regimens. Treatment cours-
es were repeated every 21 days. Patients in the CDT cohort
received oral CDT (4 tablets, 3 times a day) (Guangzhou Bai
Yunshan Chinese Medicine Co.). Patients in the warfarin co-
hort were given oral warfarin tablets (Orian Corporation, Espoo,
Finland) (1 or 2 mg, once a day) with close monitoring of pro-
thrombin time-international normalized ratio. No other an-
ti-thromboembolic agents were used during the treatment.

Treatment efficacy and safety assessments

The clinical signs and symptoms related to the VTEs in all pa-
tients, such as abnormal local swelling, pain, tenderness, tem-
perature, color, or mucosae and hemorheologic indices including

hematocrit and platelet aggregation, were carefully collected. As bleeding is the primary severe adverse effect (AE) of anti-thromboembolism, the clinical signs and symptoms related to bleeding, such as mucosal bleeding, and menstrual blood volume changes for females, were collected. Other adverse effects, including nausea, vomiting, diarrhea, itching, rash, and skin necrosis, were also carefully collected. Adverse events were graded with the use of the Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

GraphPad Prism 6.0 for Mac was used for statistical analysis. The results are expressed as mean ± standard error of mean (SEM). One-way ANOVA was used for comparisons among 3 groups. Comparisons of variables at the different time points within a group were performed using the paired t test and comparisons of variables between 2 cohorts were performed by using the unpaired t test. VTE incidence rate between 2 cohorts was compared by Fisher's exact test. All P values were 2-sided. A $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 313 MM patients treated with thalidomide-based chemotherapy (130 females and 183 males) were eligible to be evaluated. The median age was 59 years (range 29–76 years). The median treatment duration was 15 months (range 2–45 months). Based on the antithrombotic agents administered, 313 patients were divided into 3 cohorts: CDT cohort (n=130), warfarin cohort (n=94), and no antithrombotic treatment cohort (control group) (n=89). The chemotherapy regimens administered included: melphalan, cyclophosphamide, prednisone, and thalidomide (MPCT) (n=97); vincristine, doxorubicin, dexamethasone, and thalidomide (VADT) (n=93); dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide, and etoposide (DTPACE) (n=48); or bortezomib, dexamethasone, and thalidomide (BDT) (n=75). The disease status before thalidomide treatment was classified as newly diagnosed or relapsed/refractory MM. A total of 116 MM patients (37.07%) used thalidomide-based regimens as the frontline therapy, while 197 of patients (62.94%) were treated with thalidomide-based regimens while in relapsed/refractory status. Detailed patient characteristics, including immunoisotype, Durie-Salmon stage, disease status at the beginning of thalidomide treatment, duration of thalidomide use, time from the beginning of thalidomide treatment to the development of a VTE, and regular laboratory data, are summarized in Table 1. No significant differences were found among CDT, warfarin, and control cohorts based on platelet counts, fibrinogen, and D-dimer levels, as well as age, sex, MM type, Durie-Salmon stage, and administration of chemotherapy regimens (Table 2).

CDT and warfarin reduce VTE events in the MM patients treated with thalidomide-based regimens

Of the 313 MM patients treated with thalidomide-based regimens, 224 patients (71.57%) had undergone VTE prophylaxis with CDT or warfarin, and none of them developed a VTE. Seven patients (2.24%) developed VTE, all in the no prophylaxis group (i.e., 7 out of 89 patients in the non-prophylaxis group [7.87%] developed VTE). The VTE incidence rate in the control group was significantly higher than that in the CDT and warfarin groups (p=0.002 and p = 0.006, respectively). Among the 7 patients experiencing VTEs, 6 (6.74%) had deep vein thrombosis (DVT) and 1 (1.13%) had pulmonary embolism (PE), which were confirmed by venous ultrasonography and spiral computed tomography, respectively. When VTE was diagnosed, the patient was injected with low-molecular-weight-heparin, either 1 dose daily (1.5 mg/kg/day) or 2 doses daily (1 mg/kg every 12 h). Unfortunately, the patient who developed a PE during the fourth chemotherapy cycle of VADT died. Six patients developing DVT gradually recovered after anti-thromboembolic treatment.

Of 7 VTE cases, 4 were treated with a VADT regimen, 2 were treated with a MCPT regimen, and 1 was treated with BDT regimen. Collectively, 5 of 7 VTE patients (71.43%) received thalidomide plus high-dose dexamethasone therapy, and 4 of 7 VTE patients (57.14%) were treated with thalidomide in combination with high-dose dexamethasone and doxorubicin. According to the Durie-Salmon stage, 6 of 7 VTE patients (85.71%) were diagnosed with stage III (including 5 patients with stage IIIA and 1 with stage IIIB) (Table 3).

CDT is better tolerated than warfarin for long-term use in MM patients

Although no VTE occurred in the 2 cohorts with anti-thromboembolism therapy, 3 patients (3.19%) experienced hemorrhage in the warfarin cohort. One experienced gastrorrhagia, which was well controlled with iced oral administration of norepinephrine, proton pump inhibitors, and transfusion of red blood cells after discontinuation of warfarin treatment; 1 had cerebral hemorrhage, and upon warfarin termination and administering mannitol treatment, the patient improved without neurological sequelae; and 1 experienced retinal hemorrhage and recovered completely after discontinuation of warfarin and administration of CDT 2 weeks later (Table 4). There were no warfarin-associated deaths. In contrast, treatment with CDT was well tolerated, with itching and rash (n=4, grade 1, 2) being the most common AEs. There were also possibly related AEs of palpitations (n=2, grade 1 and 2, respectively) and

Table 1. Clinical characteristics and chemotherapy regimens in three cohorts of MM patients.

	Control		CDT		Warfarin		Total	
Total number of patients (%)	89	(20.00)	130	(46.43)	94	(33.57)	313	(100)
Age, median, y (range, y)	57	(32–76)	60	(29–74)	59	(34–74)	59	(29–76)
Disease status (%)								
New	34	(37.07)	47	(36.15)	35	(37.23)	116	(37.07)
R/R	55	(62.93)	83	(63.85)	59	(62.77)	197	(62.94)
Gender (%)								
Male	53	(59.55)	73	(56.15)	59	(62.77)	185	(59.11)
Female	36	(40.45)	57	(43.85)	35	(37.23)	128	(40.89)
Classification (%)								
IgA	23	(25.84)	33	(25.38)	25	(26.60)	81	(25.88)
IgG	51	(57.30)	70	(53.85)	57	(60.64)	178	(56.87)
IgM	0	(0.00)	3	(2.31)	0	(0.00)	3	(0.96)
Light chain	15	(16.85)	24	(18.46)	12	(12.77)	51	(16.29)
Durie-Salmon Stage (%)								
IA	4	(4.49)	2	(1.54)	2	(2.12)	8	(2.56)
IB	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
IIA	29	(32.58)	32	(24.62)	23	(24.47)	84	(26.84)
IIB	4	(4.49)	12	(9.23)	8	(8.51)	24	(7.67)
IIIA	44	(49.44)	70	(53.85)	50	(53.19)	164	(52.40)
IIIB	8	(8.99)	14	(10.77)	11	(11.70)	33	(10.54)
Regimen (%)								
MPCT	27	(30.34)	44	(33.85)	26	(27.66)	97	(30.99)
DTPACE	15	(16.07)	19	(14.62)	14	(14.89)	48	(15.34)
VADT	25	(28.09)	39	(30.00)	29	(30.85)	93	(29.71)
BDT	22	(24.72)	28	(21.54)	25	(26.60)	75	(23.96)

Table 2. Clinical characteristics associated with coagulation before treatment in three cohorts of MM patients.

Category	Control	CDT	Warfarin	Total
D-dimer, mg/L	0.361±0.025	0.370±0.012	0.380±0.020	0.621
Fibrinogen, g/L	2.49±0.48	2.56±0.38	2.61±0.45	0.255
White blood cell, 10^9/L	6.0±4.8	5.9±2.4	5.9±1.9	0.358
Hemoglobin, g/L	124.3±13.7	134.5±11.5	131.6±11.4	0.174
Platelets, 10^9/L	137.5±35.3	133.3±44.5	137.7±52.7	0.483

headache (n=1, grade 2). These symptoms were relieved after decreasing the dose or intervention with antihistamines in all except 1 patient (grade 3), who suffered from palpitation half an hour after taking CDT and finally stopped the CDT treatment. However, no bleeding and no other SAEs were observed in the CDT cohort.

Table 3. Clinical features of 7 patients suffering from VTE.

Patient	Sex	Age, y	Stage[a]	Type	Regimen	Week[b]	Disease status[c]	PE[d]
P1	F	58	IIIA	Lambda	VADT	9	New	Y
P2	F	49	IIIB	IgG/lambda	VADT	6	R/R	N
P3	M	71	IIIA	IgG/kappa	CMPT	10	New	N
P4	M	66	IIA	IgA/lambda	VADT	18	R/R	N
P5	F	79	IIIA	IgG/kappa	BDT	4	New	N
P6	M	69	IIIA	IgG/kappa	CMPT	7	R/R	N
P7	F	65	IIIA	IgA/kappa	VADT	8	R/R	N

[a] Durie-Salmon; [b] Duration of thalidomide therapy (weeks); [c] "New" refers to "newly diagnosed", "R/R" refers to "relapsed/refractory";
[d] PE, pulmonary embolism, "Y" refers to "yes", and "N" refers to "no".

Table 4. Clinical features of 3 patients with hemorrhage resulting from Warfarin.

Patient	Sex	Age, y	Stage[a]	Type	Regimen	Disease status[b]	Week[c]	Site of hemorrhage
P1	M	68	IIIB	IgG/lambda	VADT	R/R	12	Gastrorrhagia
P2	F	75	IIIB	Kappa	DTPAGE	R/R	16	Cerebral
P3	M	72	IIIA	IgG/kappa	CMPT	New	25	Retinal

[a] Durie-Salmon; [b] "New" refers to "newly diagnosed", "R/R" refers to "relapsed/refractory"; [c] Duration of warfarin therapy (weeks).

CDT and warfarin reduced the elevated D-dimer and fibrinogen levels induced by thalidomide-based chemotherapy

To evaluate patient coagulation status during thalidomide-based regimens and antithrombotic treatment, D-dimer and fibrinogen levels in the peripheral blood of MM patients were analyzed from pretreatment to 8 months after antithrombotic treatment. We found that D-dimer and fibrinogen levels slightly increased with oral thalidomide in the no prophylaxis cohort. However, the 2 clotting parameters gradually decreased in the CDT and warfarin cohorts. We found no significant differences among the 3 cohorts during the first 2 months of therapy.

After 3 months of thalidomide-based chemotherapy, the mean levels of D-dimer and fibrinogen significantly rose to 0.474 (±0.048) mg/L and 3.26 (±1.53) g/L, respectively, in the control group (n=83) (p=0.002 and p=0.019, respectively), and then slowly increased until 8 months (n=71). Furthermore, the mean D-dimer and fibrinogen levels were 0.79 (±0.163) mg/L and 4.25 (±1.21) g/L, respectively, in MM patients developing VTE, which were significantly higher than that in the no VTE patients receiving thalidomide-based regimens (p<0.0001 and p=0.016, respectively) (Figure 1). Notably, these D-dimer and fibrinogen levels were significantly higher than those in the CDT (n=119) (p=0.001 and p=0.008, respectively) and warfarin

cohorts (n=78) (p<0.001 and p=0.007, respectively) until 8 months of observation (Figure 2).

The D-dimer level significantly decreased from 0.380 (±0.020) mg/L at baseline (n=89) to 0.195 (±0.141) mg/L (n=88) in the warfarin cohort (p<0.001) and from 0.370 (±0.012) mg/L at baseline (n=130) to 0.289 (±0.039) mg/L (n=130) in the CDT cohort (p=0.004) after 3 months of antithrombotic treatment, and then remained relatively stable until 8 months after antithrombotic treatment in both groups (all p<0.05) (Figure 2A). In contrast, the fibrinogen level mildly decreased 3 months after treatment of the CDT and warfarin cohorts, and there was no difference between the 2 antithrombotic cohorts. However, the fibrinogen levels continued to decrease 6 months after antithrombotic treatment in the warfarin cohort, which were different from the stable levels in the CDT cohort. The fibrinogen levels significantly decreased from 2.61 (±0.45) g/L at baseline (n=89) to 1.97 (±0.42) g/L 6 months after warfarin treatment (n=81, p=0.013) to 1.54 (±0.78) g/L at 7 months (n=80, p=0.005), and to 1.46 (±0.34) g/L at 8 months (n=78, p=0.0045). The fibrinogen levels in the warfarin cohort were significantly lower than those in the CDT cohort at 7 months (n=122, p=0.006) and at 8 months (n=119, p=0.001) (Figure 2B). Although the fibrinogen levels remained at relatively low levels after 3 months of CDT treatment, no significant differences were found when compared to the baseline levels.
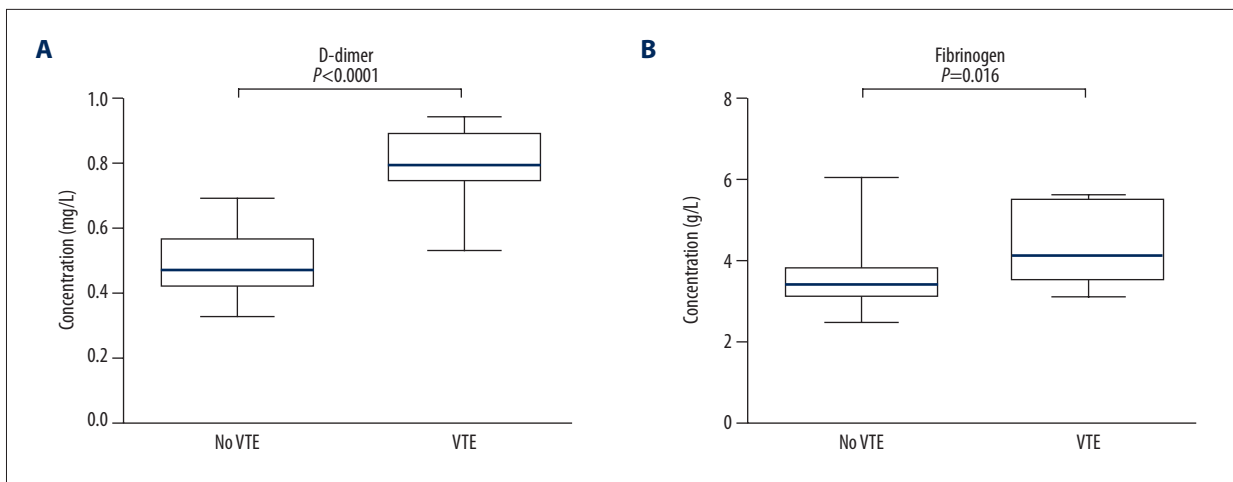
Figure 1. D-dimer and fibrinogen levels in the MM patients developing VTE *vs.* the patients without VTE during thalidomide-based regimens. (**A**) D-dimer and (**B**) fibrinogen levels significantly increased in the patients experiencing VTE when compared to the no VTE patients.

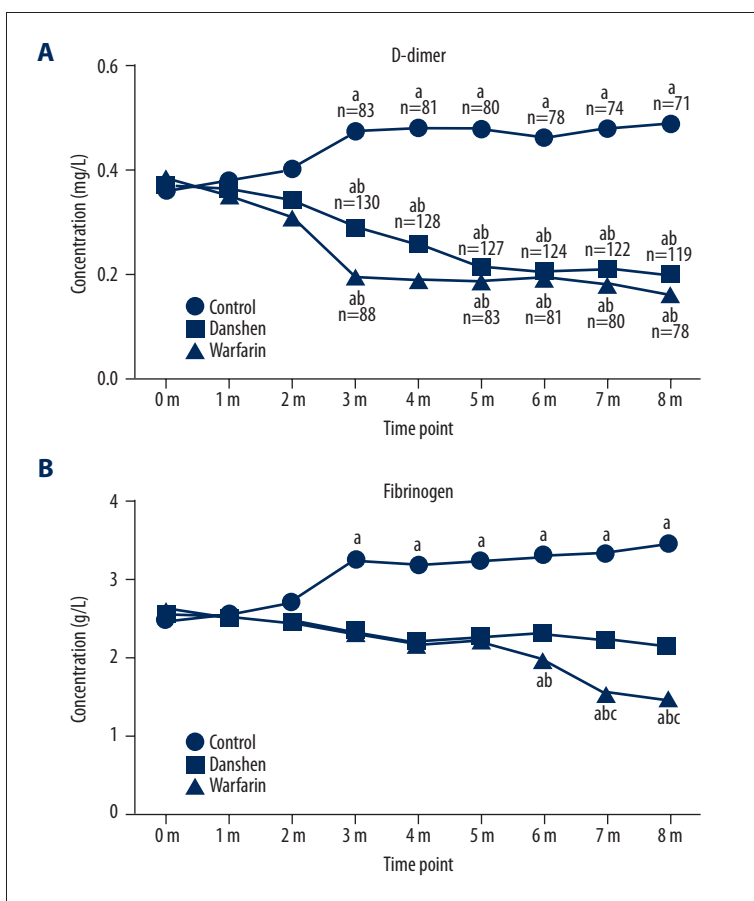**Figure 2.** Monitoring of D-dimer and fibrinogen levels in MM patients treated with thalidomide-based regimens and anti-thromboembolic agents. (**A**) D-dimer and (**B**) fibrinogen levels significantly increased in MM patients with no prophylaxis during thalidomide-based regimens. However, 2 blotting parameters were obviously decreased 3 months after CDT or warfarin treatment. "m" refers to duration of thalidomide therapy (month), and "0 m" refers to baseline. [a] $p<0.05$ compared to baseline level; [b] $p<0.05$ compared to the control cohort; [c] $p<0.05$ compared to the CDT cohort.

Discussion

In this retrospective study, we found CDT and warfarin could effectively reduce the elevated D-dimer and fibrinogen levels induced by thalidomide-based chemotherapy after 3 months of treatment. More importantly, no patients developed VTE in the CDT cohort, an anti-thromboembolism effect comparable to that of warfarin. No bleeding and on other SAEs were also observed, exhibiting its superiority in terms of safety.

Thalidomide-based regimens have undeniably improved the outcomes of multiple myeloma (MM), but increased the risk of thromboembolic events [6–8]. As shown in this retrospective study, we observed a VTE incidence of 2.24% in all of the patients investigated, and a 7.87% VTE incidence rate in the absence of thromboprophylaxis, consistent with previous reports from Asians [18], but lower than the reports from Western countries [19], where VTE incidence was highly variable among the different trials and could be as high as 58% when thalidomide was given in combination with doxorubicin and dexamethasone in the absence of thromboprophylaxis [20]. In addition, we also observed that the incidence of VTE events was associated with advanced disease, and combination of thalidomide with high-dose dexamethasone or/and doxorubicin, in accord with previous observations [19].

D-dimer, a degradation product of cross-linked fibrin, was repeatedly confirmed to be a highly sensitive and clinically useful marker for predicting thrombosis [24–26]. In this retrospective study, we observed that levels of D-dimer and fibrinogen were significantly increased in the no thromboprophylaxis cohort, particularly in those patients who developed VTE, indicating that high levels of D-dimer and fibrinogen are associated with the risk of VTE in MM patients treated with thalidomide-based regimens. Importantly, the administration of CDT could reduce D-dimer and fibrinogen levels, especially the D-dimer levels [23,27]. CDT showed a slowly reducing effect relative to warfarin, which may partially explain the distinct effects of these 2 antithrombotic therapies and the greater safety associated with the use of CDT.

Because the occurrence of thromboembolism may lead to chemotherapy discontinuation and higher health expenditure in MM patients, the risk of thromboembolic events with the use of thalidomide still should not be neglected in Asian populations, although the incidence of VTE events was lower relative to Western countries. Warfarin is the first choice in antithrombotic prophylaxis based on the antithrombotic efficacy and adverse effects of antithrombotic agents. In our retrospective study, 30.03% of patients had undergone VTE prophylaxis with warfarin and none of them experienced VTEs. However, a 3.19% incidence rate of hemorrhage was observed in the warfarin cohort [10,11], which may be associated with poor vascular walls caused by persistent hyperlipidemia and aging in MM patients. In contrast, CDT has been widely used in elderly people in Asian countries, especially in China, because it dilates coronary arteries and improves blood viscosity and microcirculation. In the current retrospective study, 41.53% of patients had undergone VTE prophylaxis with CDT; more interestingly, CDT had a comparable efficacy with warfarin for thromboembolism prophylaxis, but no hemorrhage or other SAEs were found. The possible mechanism by which CDT inhibits thrombosis may be by suppressing the expression of adhesion molecules [21]. Moreover, it was reported that tanshinone IIA (TIIA), the major lipophilic components extracted from Danshen, could have a strong anticoagulant activity by enhancing fibrinolytic activity, decreasing cyclooxygenase-2 activity [22], and inhibiting platelet aggregation [23]. Besides, Asian patients have a much higher incidence of major bleeding [10,18], in contrast to a low incidence of hemorrhage for antithrombotic prophylaxis in Western countries. This fact will undoubtedly affect policy regarding the administration of antithrombotic agents in Asia. Thus, CDT may be a better option for the prevention of thalidomide-associated thromboembolism among MM patients, and will extensively benefit the MM population by virtue of its greater safety and acceptability during long-term use.

Conclusions

These multicenter findings demonstrate that CDT is an effective therapy for the prevention of thalidomide-associated VTE among MM patients based on its clinical outcomes and laboratory prediction marker of thromboembolism risk. Further mechanistic research, rigorously designed pharmacological evaluation, and multicenter clinical trials are warranted.

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