RESEARCH ARTICLE

Analysis of Prethrombotic States in Patients with Malignant Tumors

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Abstract

Background: This study aimed to investigate the incidence and risk factors for a prethrombotic state in patients with malignant tumors. Materials and Methods: Plasma d-dimer (D-D) in patients with malignant tumors was measured. Abnormal rates of D-D and possible risk factors like gender, age, type of tumor, and staging of tumor were analyzed. Results: Of 1,453 patients, 629 demonstrated plasma D-D abnormality (43.3%). The D-D abnormal rate of male patients (n=851, 43.5%) was not statistically significantly different from that for female patients (n=602, 43.0%) ($p>0.05$). D-D abnormal rate increased with age and was statistically significant among different age groups ($p<0.05$). Regarding staging of tumor, D-D abnormal rate in patients with phaseI was 2.0%, 6.2% in phase II, 47.6% in phase III and 83.1% in phase IV, with statistically significant differences between phase III and II, as well as phase III and IV ($p<0.01$). Conclusions: A prethrombotic state was closely related to malignancy of tumors. The risk factors for a prethrombotic state include age and tumor stage.

Keywords: Prethrombotic state - malignant tumor - riask factors

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Introduction

Prethrombotic state, also known as prothrombosis state or high coagulation state refers to the dysfunction of hemostasis, coagulation, anticoagulation and fibrinolysis (Linkins et al., 2013). A previous study suggested that malignant tumor complicated by prethrombotic state is an underlying reason for thrombosis. Meanwhile, high coagulation state is associated with invasion and metastasis of malignancies (Rybicki et al., 2010; Koh et al., 2011). Lack of awareness of classical clinical features and specific reports of incidence, prethrombotic state still did not attract great attention of clinical medicine in preventing and managing high coagulation state. D-dimer (D-D) is a fibrin degradation product after fibrin monomers bound to activating factor and degraded by plasimin, which is a molecular biomarker for coagulation and fibrinolysis. High level of D-D reflects the double activation of coagulation and fibrinolysis system specifically by marking the formation of fibrin in blood vessels, which marks the high coagulation state and secondary increased fibrinolytic activity *in vivo* (Bigger et al., 1999; Jiang Z, et al., 2009). The current study aimed to investigate the incidence and related risk factors of prethrombotic state in patients with malignant tumors by detecting D-D.

Materials and Methods

General information

The total sample included 1453 patients (aged from 26-91 years) with malignant tumor, 851 male accounted for 58.6% while 602 female accounted for 41.4% and the median age was 61.1 years old. All patients were diagnosed between January 2012 and December 2013. Among them, 2 patients in age group 20-, 47 in 30-, 221 in 40-, 344 in 50-, 511 in 60-, 235 in 70-, 92 in 80- and 1 in 90-. For tumor stage, 50 patients were staged phaseI, 406 phaseII (635 phaseIII and 362 phaseIV. General characteristics were described in Table1.

Methods

Following a fasting period of 8-10h, 3mL venous blood samples were extracted from the patients and into tubes containing 1/10 volume anticoagulant Sodium Citrate Solution (0.109mo/L). The samples were centrifuged at 3000*g for 10min. The plasma samples were then separated and maintained at -20°C within 2h after blood samples collection. D-D levels were measured wityh the assistance of a Sysmex CA7000 automated blood coagulation analyzer and related reagents within 4h after blood samples collection.

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Table 1. General Characteristics of Patients

Tumor Types	Sample size (n)	Constituent ratio (%)	Male (n)	Sex ratio (%)	Female (n)	Sex ratio (%)
Prostatic cancer(PCa)	10	0.7	10	100.0	0	0.0
Primary Hepatic cancer(PHC)	46	3.2	34	73.9	12	26.1
Ovarian cancer	81	5.6	0	0.0	81	100.0
Pancreatic cancer	12	0.8	4	33.3	8	66.7
Oral cancer	13	0.9	7	53.8	6	46.2
Small cell lung cancer(SCLC)	25	1.7	22	88.0	3	12.0
Cardiac carcinoma	36	2.5	28	77.8	8	22.2
Biliarymalignant tumor(BMT)	11	0.8	7	63.6	4	36.4
Urological malignancy	16	1.1	9	56.3	7	43.8
Gastric cancer	126	8.7	92	73.0	34	27.0
Non-small-cell lung cancer(NSCLC)	296	20.4	201	67.9	95	32.1
Cervical cancer	40	2.8	0	0.0	40	100.0
Esophageal carcinoma	441	30.4	350	79.4	91	20.6
Non hodgkin lymphoma(NHL)	32	2.2	22	68.8	10	31.3
Rectal carcinoma	49	3.4	21	42.9	28	57.1
Colon cancer	47	3.2	33	70.2	14	29.8
Brain glioma	12	0.8	4	33.3	8	66.7
Breast cancer	150	10.3	0	0.0	150	100.0
Head and neck tumor	10	0.7	7	70.0	3	30.0
Total	1453	100.0	851	58.6	602	41.4

Table 2. Abnormality of D-D in 1453 Patients

Tumor Types	Smaple size	Number of abnormity	Abnormal rate(%)
Prostatic cancer(PCa)	10	7	70.00
Primary Hepatic cancer(PHC)	46	31	67.39
Ovarian cancer	81	54	66.67
Pancreatic cancer	12	8	66.67
Oral cancer	13	8	61.54
Small cell lung cancer(SCLC)	25	15	60.00
Cardiac carcinoma	36	21	58.33
Biliarymalignant tumor(BMT)	11	6	54.55
Urological malignancy	16	8	50.00
Gastric cancer	126	63	50.00
Non-small-cell lung cancer(NSCLC)	296	138	46.62
Cervical cancer	40	18	45.00
Esophageal carcinoma	441	177	40.14
Non hodgkin lymphoma(NHL)	32	11	34.38
Rectal carcinoma	49	14	28.57
Colon cancer	47	13	27.66
Brain glioma	12	3	25.00
Breast cancer	150	33	22.00
Head and neck tumor	10	1	10.00
Total	1453	629	43.29

Statistic analysis

Data analysis was performed using SPSS19.0 software. T-test was used on intra-group comparison and ANOVA analysis was performed for comparison between groups. $P<0.05$ was considered to indicate a statistically significance of difference.

Results

Abnormal rate of D-D

Abnormality of D-D was found in 629 patients with a proportion of 43.29% (629/1453). Details were presented in Table2.

D-D and Gender

The abnormality of D-D was compared between male and female. Among 851 male, 370 samples (43.5%) showed abnormality and 259 in 602 (43.02%)female samples were abnormal, no statistically significant difference was detected between gender ($x^2=0.030$, $p>0.05$).

Table 3. Abnormality of D-D in Different Age Groups

Age	Sample size	Number of abnormity	Abnormal rate(%)
20-	2	0	0.0
30-	47	14	29.8
40-	221	64	29.0
50-	344	126	36.6
60-	511	245	47.9
70-	235	126	53.6
80-	92	53	57.6
90-	1	1	100.0
Total	1453	629	43.3

Table 4. Analysis of Tumor Staging and D-D

Age	Sample size	Number of abnormity	Abnormal rate(%)
I	50	1	2.0
II	406	28	6.2
III	635	302	47.6 *
IV	362	298	83.1 *
Total	1453	629	43.3

*$P<0.01$

D-D and Age

As shows in Table3, D-D abnormal rate increase with age gradually and the correlations among groups are distinct ($F=2.224$, $p=0.038$).

D-D and Tumor stage

As Table4 shows, regarding staging of tumor, except phaseI (D-D abnormal rate=2.0%) and phaseII

Table 5. Analysis on Different Tumor Types and D-D

Tumer types		p value	Tumer types		p value	Tumer types		p value
Cervical cancer with	Colon cancer	0	Ovarian cancer with	Esophageal carcinoma	0	NSCLC with	Cardiac carcinoma	0
	Ovarian cancer	0		Breast cancer	0		Cervical cancer	0.997
	PCa	0.019		Gastric cancer	0		Colon cancer	0
	Esophageal carcinoma	0.001		Rectal carcinoma	0.13		Ovarian cancer	0
	Breast cancer	1		NHL	0.002		Esophageal carcinoma	0.021
	Gastric cancer	0		PHC	0.009		Breast cancer	0
	Pancreatic cancer	0.524		SCLC	0.002		Gastric cancer	1
	Rectal carcinoma	0		NSCLC	0		Rectal carcinoma	0.945
	NHL	0		Cardiac carcinoma	0		NHL	0.054
	PHC	0		Cervical cancer	0		PHC	0
	SCLC	0		Colon cancer	0.033		SCLC	0.031
	NSCLC	0	Esophageal carcinoma with	Breast cancer	0	NHL with	PHC	0.019
	Cardiac carcinoma	0		Gastric cancer	0.706		SCLC	0.008
Colon cancer with	Ovarian cancer	0.472		Pancreatic cancer	0.71		NSCLC	0.044
	Esophageal carcinoma	0.902		Rectal carcinoma	0.834		Cardiac carcinoma	0.007
	Breast cancer	0.172		NHL	0.021		Cervical cancer	0.024
	Gastric cancer	0.845		PHC	0		Colon cancer	0.016
	Rectal carcinoma	0.032		SCLC	0.863		Ovarian cancer	0.011
	NHL	0.006		NSCLC	0		PCa	0.393
	PHC	0.001		Cardiac carcinoma	0.95		Esophageal carcinoma	0.104
	SCLC	0.123		Cervical cancer	0		Breast cancer	0.008
	NSCLC	0.921		Colon cancer	0		Gastric cancer	0.059
	Cardiac carcinoma	0.324		Ovarian cancer	0		Pancreatic cancer	0.015
	Cervical cancer	0.002	Rectal carcinoma with	NHL	0.998		Rectal carcinoma	0.002
Breast cancer with	Gastric cancer	1		PHC	0.024	Gastric cancer with	Pancreatic cancer	0.217
	Pancreatic cancer	0.56		SCLC	0.975		Rectal carcinoma	0
	Rectal carcinoma	0.14		NSCLC	0.462		NHL	0.002
	NHL	0		Cardiac carcinoma	1		PHC	0
	PHC	0		Cervical cancer	0		SCLC	0
	SCLC	0.012		Colon cancer	0.054		NSCLC	0.798
	NSCLC	0		Ovarian cancer	0.059		Cardiac carcinoma	0.997
	Cardiac carcinoma	0		Esophageal carcinoma	0.522		Cervical cancer	0
	Cervical cancer	0		Breast cancer	0.267		Colon cancer	0
	Colon cancer	0.706		Gastric cancer	0.23		Ovarian cancer	0
	Ovarian cancer	0					PCa	0.186
	PCa	0.352					Esophageal carcinoma	0.824
	Esophageal carcinoma	0					Breast cancer	0.68

(D-D abnormal rate=6.2%), phaseIII (D-D abnormal rate=47.6%) and phaseIV (D-D abnormal rate=83.1%) had statistically significant differences ($p<0.01$).

D-D and Tumor type

Table 5 shows the comparison among different tumor types and D-D abnormality.

Discussion

Prethrombotic state, also known as prothrombosis state or high coagulation state, is a pathological state, manifesting high blood coagulation to form thromboembolism easily because of hyperfunction of hematischesis and antithrombotic (He et al., 2009). Migrating phlebitis in patients with cancer was first reported by Aramnd Trousseau in 1865, and was claimed that spontaneous clotting tendency occurred without the existence of inflammatory response, which could be called 'Trousseau Syndrome'. Studies have shown that tumor cells could undermine the balance of coagulation, anticoagulant and fibrinolytic system through multiple mechanisms, which leads to prethrombotic state. Tumor cells is reported to induce inflammatory response, release cytokine, injury vascular wall directly or indirectly by releasing tissue factor (TF) with procoagulation activity, e.g., cancer procoagulation (CP), plasminogen activator inhibitor-1 (PAI-1), human fibrinogen-like protein 2 (hfgl2), which could activate coagulation of patient and cause coagulation dysfunction. In addition, operations, radiotherapy and chemotherapy, hormone therapy, drainage-tube and some medications may also bring about high coagulation state.

The incidence rate of malignant tumor complicated by prethrombotic state is not clear. López suggested that about 50% cancer patients displayed laboratory indicators anomalies of coagulation system (López JA et al., 2009). According to Spyropoulos et al, 90% malignant tumor patients with metastasis presented abnormal coagulation state, 4%~30% patients had deep venous thrombosis (DVT) within 6~12 months of cancer diagnosis, 10%~25% patients were diagnosed malignant tumor within 3~5 yeas of idiopathic DVT and more than 75% among them were confirmed within 1 year.

Prethrombotic state exists in many diseases (Ouyang et al., 1999; Chen et al., 2012; 2014; Huang et al., 2012; Wang et al., 2012; Tan et al., 2014). The tumor types in our data covered all kinds of common solid tumors. Of all 1453 patients, 629 revealed plasma d-dimer abnormality (43.29%). Subgroup analysis based on gender showed that D-D abnormal rate for male patients was 43.5%, and for female was 43.02%, which implied that there is no statistically significant difference between gender. However, D-D abnormal rate increase with age increase, which was validated with Zeng's report (Zeng et al., 2012; Isaia, 2011). Several possible reasons are as follows. coagulation and fibrinolytic system was relatively stable in younger than in elderly patients. Incidence of chronic diseases increased and chronic hypoxia, inflammation, vascular degenerative change complicated by tumor with advancing age (Sud et al., 2009; Douma RA et al., 2010; Jaffrelot et al., 2012; Wei et al., 2012).

Our current study indicated that the incidence of prethrombotic state varied with tumor stage. The incidence rate of prethrombotic state raised with the the increasing stage of tumor and our data showed that D-D abnormal rate in phaseIis 2.0%, 6.2% in phaseII, 47.6% in phaseIII and up to 83.1% in phaseIVwith significant differences. Thus, advanced tumors are risk factors for prethrombotic state and patients of terminal malignant tumors are more susceptible to have prethrombotic state. (López et al., 2009; Sud et al., 2009)

It is generally known that prethrombotic state is closely related to thrombotic events and the incidence is as high as 4%~20%, which is the second leading cause of death of malignant tumor patients. Yan and others summarized clinical manifestations, risk factors and treatment of 40 patients with high coagulation state or thrombosis so as to find that the starting-time of thrombosis of 77.5% patients was in 2 months after high coagulation state happened. Analysis of clinic data of 20 cases of malignant tumor complicated by DVT pointed out that the total media survival time was 6.3months, the media survival time of patients whose D-D levels were twice above normal was 4.5 months and twice below normal was 7.3 months. Therefore, early diagnose and intervention of malignant tumor complicated by prethrombotic state to prevent thrombosis should be taken in clinical practice as DVT negatively impact on life quality and threaten the lives of cancer patients.

As the number of tumor patients steadily grow, it's important to judge prethrombotic state early. Partially, that has to do with thrombosis events, prethrombotic state has a close ties to metastasis on the flip side. Prethrombotic state is not only the pathological manifestation that tumor leads to, but also the key factor of tumor etiology and independent risk factor for prognosis of tumor. By the clinical study of Hu et al. on blood coagulation state of 180 malignant tumor patients, D-D level of tumor inchoate group and locally advanced tumor group had significant difference compare with the metastasis group. The D-D indicator in inchoate group, locally advanced tumor group and metastasis group shown a gradual increasing trend, which signified that the contents of plasma d-dimer associated with tumor staging. These illustrates that, on the one hand, prethrombotic state is involved in the process of tumor invasion and metastasis, which means tumor cells are aggressive. Tumor cells produce thrombotic accelerator specifically, which directly or indirectly activate coagulation process through inducing inflammatory response which feeds back onto tumor cells and leads to thrombotic accelerator releasing. Malignant cells settle into the vascular with the adhesive attraction of microthrombus to escape from immune system attack and go into perivascular tissues, which facilitate invasion and metastasis. On the other hand, prethrombotic state is strongly relevant to progression which includes tumor staging, angiogenesis formation and metastasis as well as adhesion, spreading, movement, proliferation and differentiation of cells (Farge et al., 2010).

This study demonstrated that the incidence of prethrombotic state was variable in different types of

tumor and the D-D levels of patients elevated by degrees which indicated that blood coagulative and fibrinolytic activity strengthened with the increasing of tumor staging and tumor burden thus trapped body in a vicious circle, which resulted thrombosis and tumor progression ultimately. After comparative analysis between the plasma D-D level of 0~4 weeks and 4~8 weeks before the end of 72 malignant patients who were impending death, zhang et al. found that the D-D level of 0~4 weeks significantly higher than 4~8 weeks before their last days (P=0.002). , which suggested that plasma D-D level showed increasing direction following disease progression in terminal phase of malignancies, form which they concluded that malignant progression in connection with the activation of coagulative and fibrinolytic system.

As a consequence, prethrombotic state predicts the invasion, metastasis and other malignant biological behavior indirectly. The increasing degree of it may often provide the clue of disease progression and poor prognosis. Detecting prethrombotic state promptly and primary or secondary prophylactic anticoagulation therapy specifically could reduce thrombotic events, improve quality of life and prolong survival period. Meanwhile, there are certain practical signification for anti-metastasis and improving clinical effects of anti-tumor.

Currently, several international large scale clinical trials support the validity of anticoagulation therapy. It has been shown by the MEDENOX trail that anticoagulation therapy significantly reduced the risk of DVT (Relative Risk=0.37 (p<0.001). In the meantime, PREVENT trail saw the obvious drop of incidence of DVT in anticoagulation therapy group compared with placebo group. 2.77%:4.96%, p=0.0015, Relative Risk reduced45% (ARR=2.19). In ARTEMIS trail, the incidence rate of DVT in medicine group and control group were 5.6% and 10.5% respectively. OR=49.5% (p=0.029). These 3 clinical trails consisted of 5000 cases in total. Although these data only contained 5%~15% malignant patients to allow us to discuss more concrete data, prophylatic anticoagulant therapy significantly reduced the incidence and risk of DVT, from the trails results.

A clinical trail aimed at patients with solid tumor during advanced stage who ruled out thrombosis was implemented in 2004, which randomly divided 385 cases into Low molecular weight heparin group (LMWH) and placebo group, 2 groups. After 12-week-treatment, 2 and 3-year survival rate of patients with LMWH treatment was remarkable than that in the placebo group (78% :55%60%:36%, p=0.03). In a separate study, 302 solid tumor patients without thrombosis were treated with therapeutic dose of LMWH for 2-week and half-quantity of LMWH for 4-week as maintenance therapy. Clinical follow up of these cases revealed that mortality of 12-month and 24-month were 12% and 10% respectively, while overall survival prolonged from 6.6 months to 8 months. With regard of median survival, comparing with 9.4 years of placebo group, it was 15.4 years in LMWH group (Kakkar et al., 2004). So, NCCN and ASCO recommend anticoagulant therapy for cancer hospitalized patients without contraindication.

We conclude that the prethrombotic state of malignant patients closely related to their prognosis and basic life quality because the rising plasma D-D level correlates with tumor invasion, progression and poor prognosis. Therefore, growing recommend of D-D quantitative measurement as indicator to evaluate prethrombotic state and prognosis of malignant patients. Pay close attention on the change of prethrombotic state of malignant patients to detect thrombosis as early as possible, which is of great importance to improve life quality and prognosis of advanced malignant patients.

In conclusion, the activation of coagulation is associated with tumor growth, angiogenesis and metastasis. In turn, tumor further stimulate the activation of the coagulation process. In its incubation period, malignant tumor may cause hypercoagulable state or share some common mechanism with thrombosis. If this assumption is correct, anticoagulant drugs can interfere not only malignant transformation of cells, but also tumor development (Bobek V, 2012). In clinical practice, discovering the prethrombotic state complicated by malignant tumor and giving anticoagulation therapy in time which could improve blood hypercoagulable, reduce thrombotic events, improve the quality of life and prolong survival time of patients and prevent tumor invasion and metastasis may have important implications. This may be another vital aspect of treating tumors (Ma et al., 2007; Imberti et al., 2009).

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