Review Article

Change of blood coagulation in gastrointestinal cancer before and after chemotherapy

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Abstract

The change of blood coagulation is frequently found among cancer patient such gastrointestinal cancer considered to be associated with high risk of disseminated intravascular coagulation (DIC) or thrombolic disease, and some of evidence exist that support an important relationship between blood coagulation and tumor homeostasis :clinical ,histological and pharmacological. Clinical and laboratory evidence focuses on the well-known tendency of patients with certain forms of cancer to develop thromboembolic disease (TED) and/or disseminated intravascular coagulation (DIC), commonly observed following rapid tumor lysis or surgical manipulation. The postmortem observations of platelet and fibrin thrombi in vessels draining tumors and the immunochemical demonstration of fibrin surrounding tumor cells have provided incontrovertible histologic evidence for an association between growing tumors and the end-products of blood coagulation, e.g., platelet aggregates and fibrin. The specificity of these reactions, however, remains uncertain. The positive results of pharmacologic intervention with anticoagulant drugs and/or antiplatelet agents in animal tumor models and inhuman cancer have also supported the notion that a "hypercoagulable" state associated with cancer is disadvantageous to the host. Thus, local or systemic tumor products and favors tumor spread, while interruption of blood coagulation reactions, in general, favors the host and impairs tumor metastasis. The effect of blood coagulation on the growth of the primary tumor is less well defined, with some studies suggesting a beneficial effect and others demonstrating an inhibitory effect on the tumor growth.

Keywords: coagulation, hypercoagulability, thromboembolic disease, disseminated intravascular disease

Introduction

The relation between cancer and coagulation is categorized by some mechanisms signifying that tumor biology and coagulation are closely linked processes [1]. It is now well established that activation of clotting is frequently found in cancer, typically manifesting as a low-grade disseminated intravascular coagulation (DIC) or venous thromboembolism (VTE) that could be result of cancer or its therapy. Patients with tumors of gastrointestinal tract are measured to be more prone to hypercoagulable state [2].Incidence of thrombosis is the highest in metastatic, fast growing, biologically aggressive cancers and associated with a poor prognosis [3].Tumors can cause hypercoagulability by expressing procoagulant

proteins, compromising venous blood flow by extrinsic compression of adjacent vessels, inducing production of inflammatory cytokines [3]. According to current indication, predictive biomarkers of VTE include platelet(PLT) and leukocyte (WBC) counts, hemoglobin (Hb), Ddimer (DD), and tissue factor (TF) [4].Importantly, rather than being just a trigger of increased thromboembolic events, cancer-induced hemostatic activity has been shown to promote tumor growth and cancer cell dissemination [5, 6]. Tumors activating the coagulation system are considered to behave more aggressively, with a higher risk of invasion and metastasis. High levels of circulating biomarkers resembling activated coagulation and fibrinolytic systems such as fibrinogen (F), fibrin(ogen) split products(FDP), and DD have been associated with decreased survival for several tumor types in previous studies [7, 8]. Researches on gastric cancer (GC), which is one of the most common and aggressive malignancies in humans, examining the relationship between activated hemostatic system and prognosis have yielded similar results [8, 14].

Pathophysiology of VTE in cancer

Overview of haemostatic system

The haemostatic system is a complex, multifaceted host defense mechanism that evolved to protect the integrity of the vascular system. It works in coordination with the mechanisms of inflammation and repair, producing a coordinated response. Haemostatic systems are normally quiescent and are only activated after injury. Ultimately, the coordinated haemostatic response results in the production of a platelet plug, fibrin-based clot, deposition of white cells at the point of injury, and activation of inflammatory and repair processes. After injury and vessel vasoconstriction, reduced blood flow permits contact activation of platelets. Subsequently, platelets adhere to exposed connective tissue (mediated in part by the von Willebrand factor) and release an array of vasoactive proteins that interact with other platelets and leukocytes, enhancing platelet activation and leading to the formation of platelet aggregates to form the initial platelet plug. At the same time, the vascular endothelium moves from its resting phase (anticoagulant) to a more active (procoagulant) and repair phase. In concert with these cellular changes, inactive plasma coagulation factors are converted to their respective active species by cleavage at internal peptide bonds. In sequence, theses (to stabilise the platelet plug), cross-linking of fibrin (through

activation of factor XIII), further activation of platelets, and activation of fibrin lytic pathways (to enable plasmin to dissolve fibrin strands in the course of wound healing). In addition, thrombin interacts with other non-haemostatic systems to promote cellular chemo taxis, fibroblast growth, angiogenesis, and wound repair.

Coagualtion Cascade:

The key role of the coagulation cascade is the production of fibrin the meshwork that holds together the clot which is produce through a cleavage of fibrinogen by thrombin. Coagulation is initiated by tissue damage, exposing the transmembrane glycoprotein tissue factor (TF). Tissue factor is expressed on the sub endothelial surface of blood vessels and is normally exposed only when normal vasculature is disrupted. Factor VII binds TF, and the TF–factor VII complex directly activates factor X to factor Xa and some factor IX to factor IXa. In the presence of factor Xa, tissue factor pathway inhibitor (TFPI) inhibits further generation of factor Xa and factor IXa. After inhibition by TFPI, the amount of factor Xa produced is insufficient to maintain coagulation. Additional factor Xa (which allows haemostasis to progress to completion) can only be generated by the factor IX–factor VIII pathway. Enough thrombin exists at this point to activate factor VIII, and together with factor IXa (generated by TF–factor VIIa) to further activate factor X. Factor IX activation is also augmented by thrombin activation of the factor XI pathway. Without the amplification and consolidating action of factor VIII/factor IX, there is insufficient generation of factor Xa to produce sufficient thrombin. When sufficient thrombin is generated, this endolytic serine protease selectively cleaves the Arg–Gly bonds of fibrinogen to form fibrin, releasing fibrinopeptides A and B and so forms the meshwork of the clot. It is of note that the above physiological description omits the classic extrinsic pathway (factor VII-TF initiated coagulation to common pathway at factor X) and intrinsic pathways activated by factor XII (and through factors XI, IX, and VIII to common pathway at factor X). Although factor XII has no role in physiological blood coagulation, it has been considered that it may have a role in cancer-related thrombosis (see below). Indeed most, if not all, aspects of the complex integrated haemostatic system have been considered to function pathologically in the setting of cancer.

Diagnosis techniques

1. Base on clinical and laboratory evidence

Thromboembolic disease

The association between neoplastic disease and thromboembolic disorders has been known since1865, when Armand Trousseau first informed a high incidence of venous thrombosis in a series of patients with gastric carcinoma.[9] In the ensuing century, a number of clinical and postmortem studies appeared describing arterial and venous thrombosis, migratory thrombophlebitis, pulmonary embolism, nonbacterial thrombotic endocarditis, and, paradoxically, bleeding in association with a wide variety of malignant tumors.[10]the overall incidence of clinical TED in patients with cancer has been reported to vary between1% and 11%! [11,13] The incidence of TED in postmortem studies of cancer patients is considerably higher.[14,15]In one prospective study, Ambrus and associates[14]reported that thrombosis and/or bleeding was the secondmost common cause of death in hospitalized cancer patients. Although patients with mucin-secreting tumors of the gastrointestinal tract have long been known to be prone to thromboembolic complications, [15] other tumor types are also associated with an increased risk of TED. Table 1 lists the estimated frequency with which carcinomas arising in different sites have been reported to be associated with clinical TED. Although pancreatic carcinoma has been associated historically with the greatest risk of TED[10,15] (up to a 50-fold increase over control subjects with pancreatitis or an incidence rate of 57%)[16] the total number of cases of TED is now higher in patients with carcinoma of the lung simply because of the greater prevalence of that tumor. Thus, the association of TED with specific tumor types may change in time as a function of many variables, including tumor prevalence, chemotherapy, and improved noninvasive techniques used for the diagnosis of TED. Indeed, a recent report detailed a series of 433 patients with breast cancer treated with chemotherapy, in whom the mci-dence rate of TED detected clinically was 5%. [17]After chemotherapy was discontinued, no patient developed thrombotic complications. Similarly, prostatic carcinoma has not been associated with a significantly increased risk of TED de novo. [16] However, such patients appear to be at increased risk when treated with either estrogen or chemotherapy. [18]Accounting, perhaps, for the 35 cases of TED in patients with prostate cancer reported in surgical procedures likewise increase the risk of TED in patients with cancer to a greater extent than in patients with nonmalignant conditions. Thus, Pines and colleagues reported that 10 of 30 patients with cancer developed deep venous thrombosis following abdominothoracic surgery, as opposed to only 14 of I 34 control subjects undergoing similar procedures for nonmalignant disease (p < 0.005).[19]

Distribution of Tumor Type in 547 cases of cancer

Association with clinical thromboembolic disease

Table 1

Tumor type	Number of cases	Frequency of tumor type %
Lung	139	25.6
Pancreas	94	17.4
Stomach	91	16.8
Colon	82	15.2
Prostate	35	6.5
Ovary/uterus	34	6.3
Gallbladder	15	2.8
Breast	11	2.0
Kidney	2	0.4
Other and unknown primary	37	7.0
Total	541	100.0

*extracted from reference 10-16

Abnormalities of blood coagulation

This increased incidence of TED has lead several authors to examine various aspects of the coagulation system in patients with cancer. Abnormalities of routine tests of blood coagulation have been reported to occur in as many as 92% of patients with cancer.[20,21]The most common clotting abnormalities in cancer patients are high levels of fibrin/ fibrinogen degradation products .[20,22] thrombocytosis [24], and hyperfibrinogenemia[20,25] . These abnormalities are consistent with the presence in cancer patients of overcompensated intravascular coagulation with fibrinolysis" (ICF).[27] In this situation, it is theorized that low-grade intravascular coagulation with accelerated clotting factor utilization is accompanied by increased synthetic rates for fibrinogen, clotting factors, and platelets, resulting in actual rises in their levels in the circulation. None of these test results, however, reflects the real kinetics of blood coagulation factors or platelets in such patients, and thus, they provide only limited information. Direct or indirect evidence supporting the presence of overcompensated ICF in these patients does exist. An increased rate of fibrinogen turnover, [28, 30] an increase in plasma levels of fibrinogen/fibrin-related antigen, [31] and an increase in plasma levels of fibrinopeptide-A (FPA) The increased FPA levels correlate with fibrinogen turnover rates in cancer patients,[30]providing further evidence that fibrin generation occurs at an increased rate in such patients. Persistent elevation of FPA levels in individual patients suggested treatment failure and a poor prognosis. It should be noted that in spite of this evidence for the common occurrence of low-grade ICF in cancer patients, the occurrence of overt DIC, characterized by consumption of platelets and clotting factors with resultant bleeding complications, is rare. In patients with other types of cancer, fulminant DIC is observed principally in patients who have mucin-secreting adenocarcinomas [40, 41] or predisposing conditions, such as gram-negative sepsis or liver impairment. [42] Thus, although subclinical DIC is common in cancer, DIC of clinical significance occurs only in 9%-15% of patients with cancer, including those in whom cytotoxic therapy maybe of importance in the production of coagulation dysfunction. [24, 41, 43]

Quantitative and Qualitative Abnormalities of Platelets in Patients with Cancer

Thrombocytopenia, occur with increased frequency in patients with cancer. Although thrombocytopenia has been described in as many as 27% of patients with cancer, [43] more conservative estimates, which exclude the effects of chemotherapy and radiation, vary from 4% in patients with inoperable lung cancer[21] to 1 1% in a large series of patients with a variety of tumors.[20] While the pathogenesis of thrombocytopenia in these patients is uncertain, several studies have documented either increased platelet destruction[44,48] or evidence for in vivo platelet activation and released. [44,48] In view of the ability of tumor cells to induce thrombocytopenia in experimental animals and platelet aggregation in vivo and in vitro, it is tempting to postulate that thrombocytopenia is also a manifestation of tumor-induced DIC. Thrombocytosis, which occurs much more frequently in untreated patients with cancer (30%60%),[20,21,23.24] may also be explained by the existence of low-grade DIC, thrombocytosis and Indeed, thrombopoietic activity has been recovered from the serum of patients with cancer and thrombocytosis,[49] suggesting the existence of an aberrancy in the usual relationship between platelet count and the production of thrombopoietin in some individuals with cancer.

Qualitative abnormalities of platelet function have been described in cancer patients [24] and have been attributed to the presence of elevated levels of fibrin (ogen) degradation products. However, no evidence can be found that supports a relationship between abnormalities of platelet function and elevation of circulating levels of FDP. Moreover, since prospective studies of platelet function in untreated cancer patients have not been performed, it is difficult to determine the true incidence of primary thrombocytopathy (excluding the effects of chemotherapy on platelet function). A more detailed consideration of the platelet response to tumor cells and their products appears in a subsequent section and in several recent reviews. [50, 51]

Base on histologic evidence

In 1 878, Billroth first reported his autopsy observalions that human tumor cells were found frequently in association with thrombi. Dvorak and associates examined the early events following intraperitoneal injection of the strain-specific TA3-Stmammary adenocarcinoma in mice. [52] Within 3 hr. of tumor injection, the peritoneal cavity contained large numbers of neutrophils and tumor cells, with smaller numbers of normal macrophages. After 12 hr., macrophages were increased in number and electron

microscopy showed evidence of "macrophage activation. "After 24 hr, no viable tumor cells remained, and the peritoneal exudate was dominated by aggregates of macrophages and lymphocytes, with an abundant fibrin deposit located on the surface of the macrophages. Similar results have been observed following implantation of either the line I or the highly malignant line 10 bile duct carcinomas in guinea pigs.[53]Gelatinous material rich in fibrin was observed shortly after tumor implantation in the subcutaneous spaces (Fig. I). Initially, the gel was relatively a cellular, but after several days, an infiltrate of neutrophils and monocytes was observed. In the line I tumors, an exuberant inflammatory reaction led eventually to replacement of the fibrin gel by connective tissue and, subsequently, tumor rejection. In the line 10 tumors, the fibrin gel developed to a lesser extent, the inflammatory response was less dramatic, organization did not occur, and tumor growth was not limited. Similar histologic evidence for the association of platelet thrombi deposited in proximity to growing tumor cells has been detailed and supports an important role for platelets (and platelet products) in the process of tumor growth. [54, 60]

These observations have led to the postulate that the interaction of tumor cells, platelets, and perhaps, inflammatory cells leads to the generation of this per tumor "fibrin gel," which is critical to the pathogenesis of tumor growth and metastasis formation. [34,50,51,52,] While many investigators have suggested that fibrin acts as a "glue," facilitating tumor cell adhesion to the endothelium, others have maintamed that tumor cells adhere independently to the endothelium, produce micro injury and secondary platelet adhesion with fibrin deposition. [57,58,61,62] Even in the absence of endothelial injury, however, sequestration of fibrinogen and [49]Cr-labeled platelets can be found at the sites of metastasis of some animal tumors.[55] The relative importance of the contribution to fibrin formation of each of the components of the hemostatic system remains the subject of intense speculation in several recent reviews.[61,68]Thus, in spite of strong histologic evidence for the association between tumor cells, inflammatory cells, platelets, and fibrin thrombi, the pathophysiology and precise sequence of events remain uncertain.
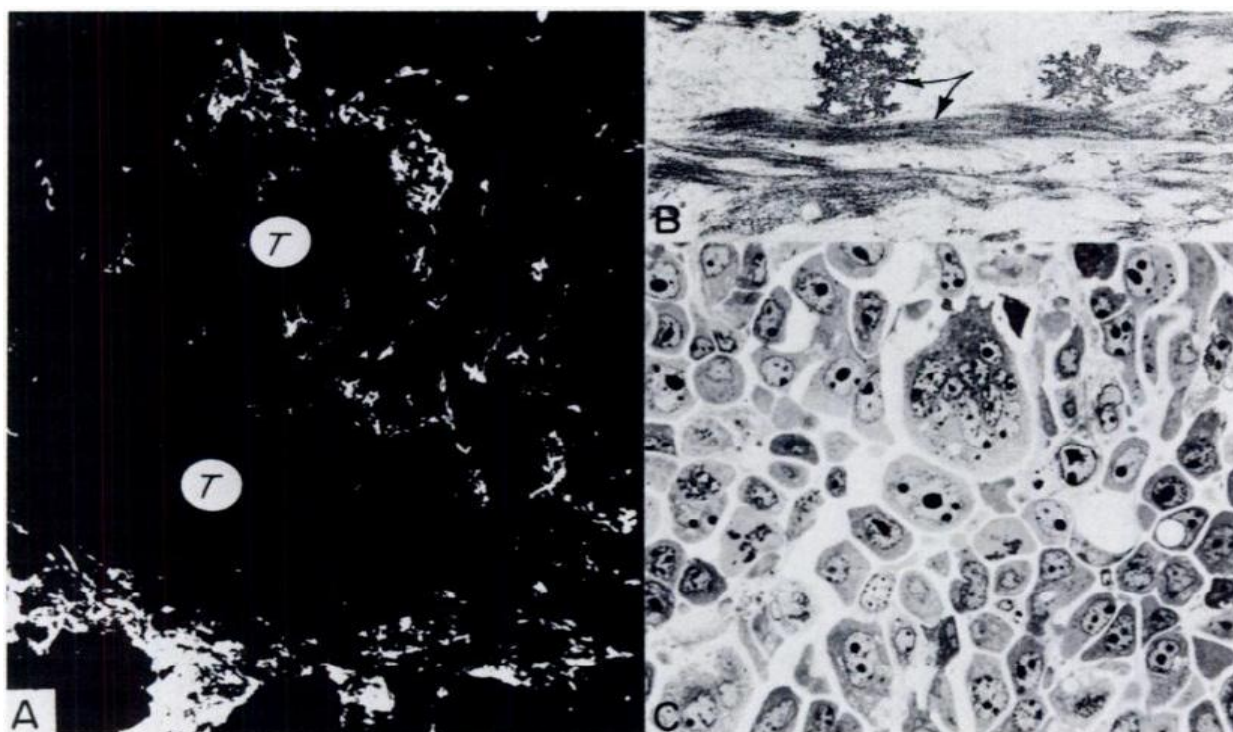

Fig .I Photomicrographs of line 1 0 tumor growing in the subcutaneous space of sensitized strain 2 guinea pigs 5 days after transplantation.(A) Immunofluorescence staining of a frozen section with fluorescein-labeled anti-guinea pig fibrinogen. Fibrin forms a thin investment about growing tumor (T). (B) Electron micrograph of fibrin investment, revealing three-dimensional meshwork of fibrin strands (arrows). (C) One micrometer thick, Epon-embedded, Giemsa-stained section illustrating morphology of the line 1 0 tumor.(Reprinted with permission.

Pharmacologic evidence -Effects of anticoagulant

Antiplatelet Agents

Support for the use of antiplatelet drugs and agents designed to produce thrombocytopenia in the treatment of cancer derives from the experimental and clinical observations reviewed above. Antiplatelet antibodies, capable of inducing thrombocytopenia, can reduce significantly the formation of lung implants following the intravenous infusion of TA3 tumor cells in mice. [77]The protective effect can be reversed with platelet transfusions. [78]Drugs that impair platelet function have also proved successful in the treatment of cancer in experimental animals (Table 2). The cytooxygenase inhibitors, aspirin [70,79,81] and indomethacin [82,83] are both capable of acting as antimetastatic agents, as are the phosphodiesterase inhibitors, dipyridamole,[84] RA-233,76 and pentoxifylline.[85] Pretreatment of mice with the potent platelet function inhibitor prostacyclin (PGI2), for example, has produced a striking reduction in the number of lung implants following injection of B16amelanoma cells into syngeneic mice. Liver and spleen "metastases" were totally prevented in recipient animals.[86,87]Aspirin and indomethacin have been effective even when given to animals 1 or 2 wk following tumor cell inoculation.[81,83] However, not all experimental tumors respond to all platelet function inhibitors. Negative results have been reported with the use of aspirin for the treatment of the V2 carcinoma inhabits and the use of aspirin, RA-233, bencyclan, orcyproheptadine for the treatment of Lewis lung carcinoma (3LL) in mice. [89] Moreover, results obtained using models such as these, in which "metastases" are induced by intravenous injection, may not prove relevant to the treatment or prevention of spontaneous metastasis formation. Finally, since thromboxane inhibitors and prostacyclin can modulate directly the growth of tumor cells in vitro, [90] the effects of these mediators on platelet function may have little to do with their antitumor properties. Trials of these drugs in human subjects have been limited. Only preliminary data from nonrandomized and/or uncontrolled studies have been published. In group of 38 patients with tumors of the head and neck, RA 233 reduced the recurrence rate and frequency of metastasis formation when compared with historic controls. [91]The results of the animal studies previously reviewed and preliminary data from humans have stimulated the organization of additional studies in patients with cancer. Several randomized controlled studies of antiplatelet agents in the treatment of venous human tumors are now in progress. [51,92] No data are yet available from these cooperative trials.

Anticoagulant

Administration of high doses of an antibody to fibrin fragment E has been used successfully in the induction of complete regression of an experimental hepatoma(line 10) in guinea pigs.[92] Although antibody was not injected until either 6 or 16 days after the animals were innoculated intradermally with tumor cells, no evidence of tumor was found in the treated animals when biopsies of the injection sites were examined at day 35.All treated animals were alive and without visible tumor at 180 days, while all of the control animals, who received normal rabbit lgG, were dead of tumor progression by day 90. None of 8 immunized animals who were rechallenged with line I 0 cells developed tumors at the site of injection. Although the mechanism of action of the antibody used in this intriguing study is not at all clear, the authors suggested that the antitumor effect observed was "presumably a consequence of its interaction with the disulfide knot region of fibrinogen, fibrin monomer, or fibrin polymer at the tumor site. [92] Indeed, other experimental approaches to the inhibition of fibrin deposition or polymerization have been successful. The timing of the therapeutic intervention, however, may be critical, depending on whether the end-point is the arrest of growth of primary tumors as opposed to the prevention of metastasis formation. For example, use of the thrombin-like enzyme batroxobin to defibrinate mice 1 days after implantation of 3LL tumor cells resulted in a decrease in pulmonary metastases with no change in the size of the primary tumor. [93] Defibrination of the animals prior to tumor implantation, however, produced an increase in pulmonary metastases with no change in the size of the primary tumor. These results led the authors to suggest that formation of peritumor fibrinin the early phases of tumor growth may be beneficial, preventing the egress of tumor cells from the primary tumor to distant sites. In contrast, fibrin formation at metastatic sites may be harmful, favoring implantalion. The inhibitory effects of anticoagulant drugs on various properties of tumor cells have been recognized for at least 30 yr. since Strauss and Saphir first reported the effects of the vitamin K antagonist dicoumarolon circulating carcinoma cells in rabbits.[94] Coumann derivatives can inhibit tumor cell locomotion, metabolism, lung colony formation, and the development of spontaneous metastases in

various experimental tumor systems.[94,102] The results of these animal studies have been reviewed recently.[74,75,103] It would appear that the effects of coumarin drugs in the treatment of cancer are mediated by their ability to interfere with the utilization of vitamin K, since administration of vitamin K promptly reverses the salutary effects[96,100] and experimental vitamin K deficiency provides similar protection from metastasis formation.[100,101] While it is tempting to conclude that the antitumor effect of warfarin is related to its inhibition of vitamin-K-induced postnibosomal modification of plasma coagulation factors, recent evidence suggests that vitamin K also may be of importance for the expression of other biologic functions of cells. Indeed, warfanin anticoagulation in vivo has been shown toreduce the in vitro expression of procoagulant activity by human monocyte [104,105] and 3LL tumor cells recovered from C57BL/6J mice.[106] Moreover, treatment of mice with a human prothrombin complex concentrate, which reversed the plasma anticoagulant effect of warfanin, failed to reverse the protection from metastases enjoyed by warfarin-treated animals.[101] In an attempt to find an alternative mechanism for the effect of warfarin, Maat turned to the macrophage as a potentially important target cell, active in both cellmediatedcoagulation and tumor cell killing. Inhibition of macrophage function in C57BL/Rij mice, accomplished by the administration of either carrageenan or silica, was effective in abolishing the protective effect of warfarin.[102]these data suggest that the antimetastatic effect of warfarin may be mediated, in part, by selective effects of warfarin on monocyte-macrophage function. Further details of this alternative hypothesis are described below. It should be noted, however, that other inhibitors of blood coagulation have antimetastatic properties in experimental tumor models. Potent tumor growth suppression has been observed following the use of heparin[107,109] other sulfated polysaccharides[110] and fibrinolytic agents[111]all of which act presumably by impairing fibrin deposition or accelerating fibrinolysis. Human studies of defibrinating agents, anticoagulants, or fibrinolytic drugs in cancer have, until recently, been limited to uncontrolled nonrandomized trials in heterogeneous groups of patients. [112] However, the results of the Veterans Administration Cooperative Study on the use of warfarin in the treatment of small cell carcinoma of the lung (SCCL), the first randomized controlled study of this agent as an anticancer drug, were recently published.[113] The median survival of patients who received warfarin in addition to standard chemotherapy (50 wk) was significantly greater than the median survival of subjects who received chemotherapy alone (26 wk, p = 0.026). The median length of time to evidence of tumor progression was also increased significantly in the warfarin group (p = 0.03). Although the results of this study are consistent with the hypothesis that warfarin interferes with local fibrin formation and tumor growth, no consistent relationship was demonstrated between the degree of hypoprothrombinemia and therapeutic effect.[114]Thus, it is possible that the beneficial effects of warfarin might have been related to other properties of the drug. In addition, the small size of the study (50patients) and the negative results of another randomized study of warfarin treatment of SCCL [115] indicate the need for caution in the interpretation of the results of the VA Cooperative study. Further studies of warfarin the treatment of larger numbers of patients with SCCL are now in progress, and results should be forthcoming.

conclusion: changing of the blood coagulation is found frequently among cancer patient such gastric cancer which have ability to develop the disseminated intravascular disease or thromboembolic disease ,in our study we found that the change of the blood coagulation is not only because of the cancer itself there is also many factor which contributed to the coagulation of the blood ,also there is many paper shows the relationship between the cancer and blood clot ,and also in our study we have found the significant role of the chemotherapy in the cancer patient specifically gastric cancer patient from here we have a clear view that the development of the blood coagulation can be as the cancer itself or can be as the result of the chemotherapy

Conflict of interest: None

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