



Plasma Fibrinogen Concentrations in Patients with Solid Tumors and Therapeutic Improvements by Combining Anticoagulants or Fibrinolytical Agents

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Abstract

Many of patient's deaths with solid tumors are caused by altered pathogenesis coagulation cascade components and processes in clinics. Therapeutic actions for inhibiting cancer coagulation complications in clinics are indispensable part of modern cancer therapies. This editorial discusses the relationship between plasma/solid tumor fibrinogen levels and mechanisms of action by anticoagulants and fibrinolytic agents. Revisit old theory with latest hypothetic and therapeutic options. Many updating clinical information between fibrinogen malformation and its specific therapy are highlighted herein.

Keywords: Cancer therapy; Assistant therapy; Fibrinogen; Blood thrombosis; Warfarin; Heparin; Oxalysine

Introduction

Cancer is one of the commonest diseases that claims about 7-10 million people mortality annually in the world. As a result, cancer remains to be a great medical challenge worldwide [1-3]. Generally speaking, many efforts and novel therapeutic interventions can impact the overall therapeutic efficacies and outcomes of cancer treatments. One of these efforts is assistant cancer therapy. Thus many assistant therapies will be offered to the cancer patients who have some serious coagulation complicate symptoms and escalations [4-6]. After a long silence, many recent findings have reemphasized that assistant cancer therapies are important options for ameliorating deadly symptoms and finally prolong patient's survivals in many clinical circumstances, aggressive disease progressions and even remote metastases.

Panorama of fibrinogen-related assistant cancer therapies

As an unfavorable clinical coagulation complication, venous thromboembolism causes a lot of cancer patient's deaths in clinics, especially in patients with advanced solid tumors [4]. Anticoagulants (AC) and/or fibrinolytic agents (FA) such as warfarin, heparin or oxalysine, etc have been designed for counteracting these adverse coagulation complications [5-11]. The possible mechanisms of action for promotion of solid tumor growth and disseminations by fibrin/fibrinogen related pathways have been partly given by Prof Dvorak (Harvard University, Boston, USA) [9,10] as:

- (i) It may form a scaffold to which tumor cells can attach a tumor stroma.
- (ii) Form a cocoon to shield tumor cells from attack by activated lymphocytes.
- (iii) It may help angiogenesis in tumor tissues.

Many coagulation-related drugs and therapies were designed and observed in experimental studies and clinical evaluations (Figure 1) [8].

Overview of fib-related assistant cancer therapies

Since blood coagulation systems and fibrin/fibrinogen matrix surrounding solid tumors are too complicated to be completely elucidated herein, many pathogenic cascade pathways can be targeted differently in each cascade stages. The relationship between drug therapeutic efficacies, coagulation cascade molecular components, mechanisms of action, pharmacological pathways and different therapeutics are depicted in Table 1 [11]. These mechanisms of action studies of drugs can be translated into different therapeutic paradigms and promoted in future.

Plasma fib concentrations (PFC) increases in clinics

Increased PFC in patients with advanced solid cancers was initially discovered and reported by the end of last century [12]. However, more recently (after 2004), PFC testing in clinics has been undertaken in more hospitals worldwide [13-19]. Further relationships between PFC, therapeutic outcomes and patient's prognostics have been proposed [13-19]. These arguments or new findings are outlined as following topics (Figure 2):

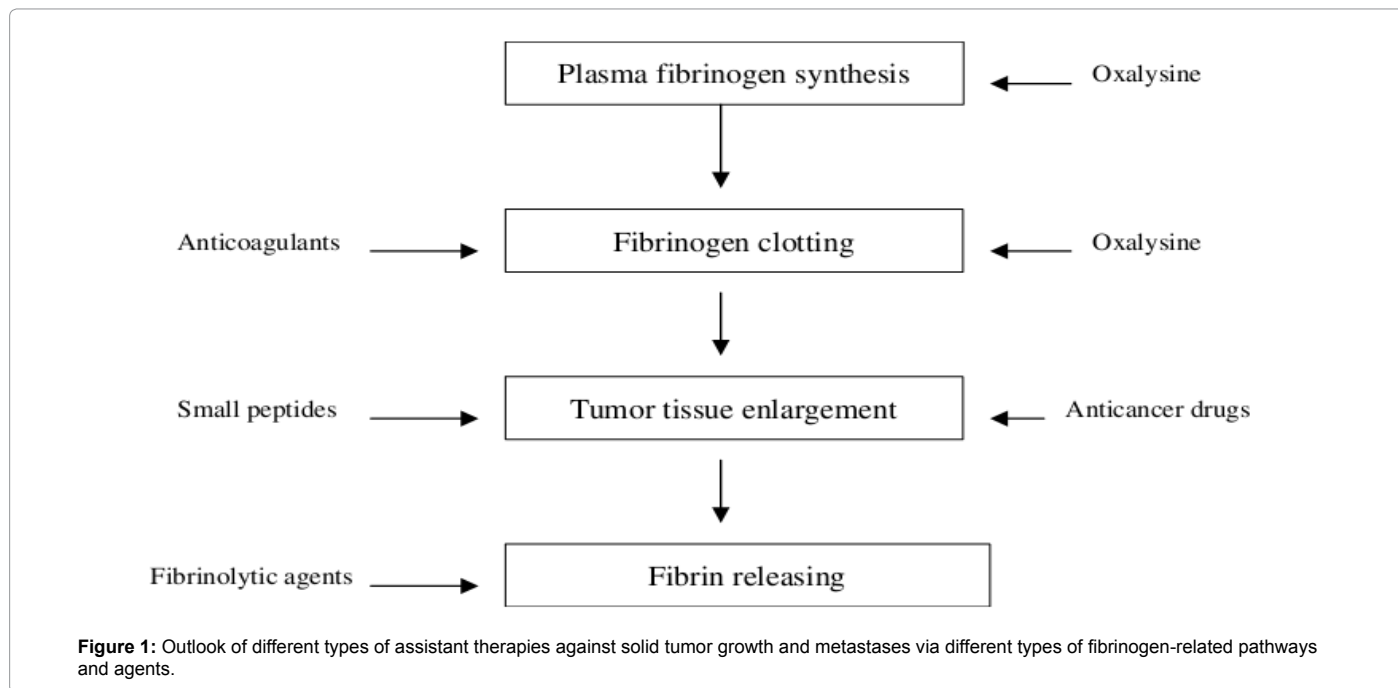
1. Whether there are differences among different stages of cancer patients (TNM)? [15,19]
2. Whether there are differences among major solid cancer categories or tumor origins? [19]

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Drug	Main biological and pharmacological targets and pathways
Heparin and its derivatives	Fibrin/fibrinogen clotting Venous thrombosis
Warfarin	Blood coagulation Venous thrombosis
PG activators	Fibrin fragment releasing Fibrin clotting breakdown
Urokinases	Fibrin clotting breakdown
Proteases	Fibrin/fibrinogen breakdown
Small peptide	Tumor/fibrinogen binding
Oxalysine	Fibrin/fibrinogen clotting Tumor/fibrinogen binding Thrombin activity Tumor-induced plasma fibrinogen level escalations
Anticancer drugs	Tumor/fibrinogen binding Fibrinogen synthesis in tumor tissues

Table 1: Overall mechanisms of action for anticancer drugs against solid tumors via fibrinogen-related pathways.

- Whether there is difference between benign and malignant cancer patients? [18]
- Whether there is a solid relationship between PFC data and therapeutic types/options? [13,19]

These arguments and new findings must be subjected into further verifications owing to its clinical significances.

New insights into different coagulant modifiers and agents in clinical cancer trials

A lot of articles have reported the possibility and capability of AC and FA on solid human cancer treatments [19-29]. The causes of disordered coagulation in patients with solid tumors can be multi-factorial events, such as neoplasm metastasis, chemotherapy or hormone therapy (impairing the blood vessel walls or promoting coagulate cascade), venous catheters using and immobilization and etc [4,5]. Moreover, disordered coagulation can be caused by multiple blood components, such as platelet [20], plasma and tumor matrix of fibrinogen levels [13-20] and the rest of coagulant components-coagulating factors (from 1 to

13) such as calcium, thrombin and plasminogen etc. [6-10,13-20]. Most importantly, cancer patients with venous thromboembolism symptoms have been given assistant therapeutic agents of AC and/or FA, mostly by warfarin, heparin, tissue plasminogen activator or oxalysine for prolonging the cancer patient's survivals greatly. Originally, AC or FA is assumed for targeting all types of solid tumors clinically. Yet the therapeutic outcomes of solid tumor treatments are sensitive by Fib-related pathway inhibitors (AC or FA) in varied tumor types, origins and stages [6-11]. From present understanding, 1/3 human solid tumors are sensitive to AC agents, and other 1/3 human solid tumors are sensitive to FA agents [8-10]. The rest 1/3 human solid tumors are insensitive to both AC and FA agents of currently licensed. Despite these discoveries, building the relationship between Fib and its related therapeutic options is important avenue for updating assistant cancer therapies. Cancer patients who undergo surgery are at high risk of developing a thromboembolic complication. Cancer patients undergoing a surgery have twice the risk of postoperative deep venous thrombosis (DVT) and more than three times the risk of fatal pulmonary embolism than patients who undergo surgery for benign diseases. Thus, promotions

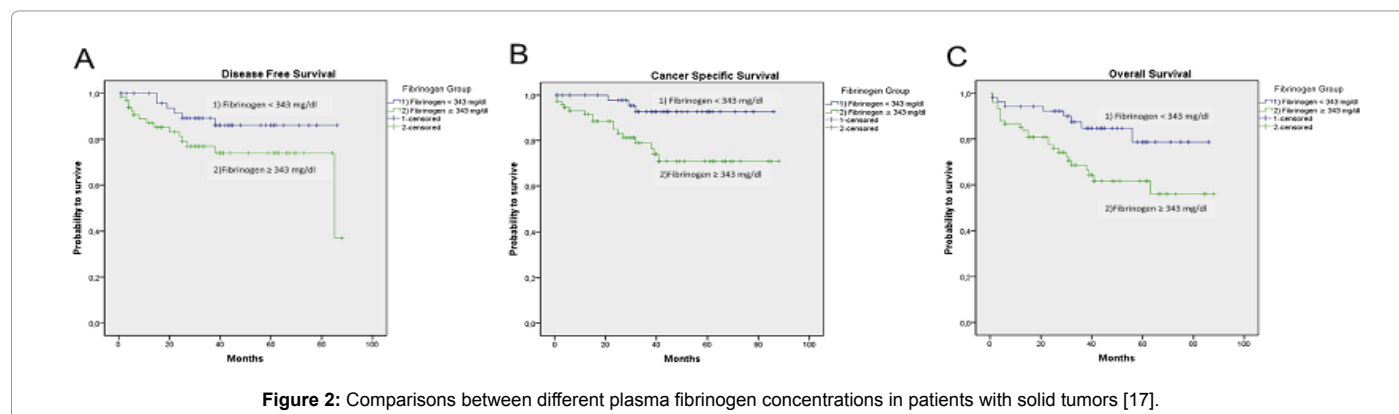


Figure 2: Comparisons between different plasma fibrinogen concentrations in patients with solid tumors [17].

of assistant cancer therapy in surgery cancer patients are necessary. In non-surgery cancer patients, prophylaxis antithrombosis therapy can be used in cancer patients with a central venous catheter, because central venous catheters will frequently increase the incidence of deep venous thrombosis (DVT) and cancer patient's deaths [7]. Since anti-thrombosis therapies are assistant therapies, AC or FA agents alone are seldom greatly useful. Common anticancer drugs are still the mainstay of conventional cancer therapies and they are more or less cooperatively active on both tumor progressions and body's coagulation system [19-29]. Conventional first-line anticancer drugs can affect the binding of fibrinogen with tumor cells and in the same times contribute to blood coagulation changes (up or down) in cancer patients overall [20,21]. To conclude, anti-thrombosis therapy must be combined with anticancer drugs. Otherwise, the therapeutic outcomes for patients with advanced solid tumors will be greatly compromised or even useless. PFC detection in clinics is very cheap (approximately 1 USD for each patient in China). Furthermore, most FA or AC agents are also low price, effective and low toxicity. Thus, this therapeutic strategy, as we can see, has a great potentiality and therapeutic significance. Comparing high costs of common anticancer drugs caused by growing expenses of drug developments or licensing in developed countries (1-1.8 billion in US) [30-32], this type of assistant cancer therapy might prove to be a cost-effective therapeutic option worldwide. It is convenient and mostly useful for many types of solid tumor treatments and disease controls for high therapeutic index.

Discussion

Since Fib, a major clotting component in human blood plays pivotal roles in the coagulation system, cancer matrix and angiogenesis formations in solid tumors can be unique therapeutic target for solid cancer treatments. Fib imbalance is associated not only with coagulation malfunctions, which complicate coronary disorders and obesity, but also with some equally fatal diseases such as solid tumors and neoplasm metastasis in clinics. Controlling the Fib overproductions by AC or FA has long be explored for promoting therapeutic efficacies against solid tumor growths and neoplasm metastasis in clinics [8]. Now a lot of clinical studies for Fib-related prognostic predictions and therapeutic interventions (options) have been frequently reported, repeat and reviewed. The biggest advantageous of conventional FA or AC treatments is very limited toxicity comparing with other types of anticancer drugs in cancer patient's treatments, which is a good quality for successful cancer therapy. Owing to this character, therapeutic efficacies/ toxicity (therapeutic index) should always be high in clinics and welcomed by cancer patients. Many AC or FA agents are biological molecules, which are very specificity to tumor metastatic pathways but less inhibitory

efficacies for large volume of tumor tissues. How to solve this drawback of AC or FA is an open question. One of these possibilities might be combined with biological AC or FC with highly cytotoxic chemicals [4-11]. Optimizing admixtures of different types of drugs should never be overlooked as presently. The different drug combination systems and rules should be focused because current drug combination strategies are based on empirical rather than science-guided strategies [33,34]. This phenomenon leads to greatly compromise therapeutic efficacies and outcomes by present drug combination strategies in clinics. Invitation of more clinicians into the systematic study of this strategy is the useful steps to completely overcome all the limitations of present assistant cancer therapy in clinical solid cancer trials.

Future perspectives

Fibrin/fibrinogen accumulation and releasing in solid tumors is a long discovered clinical event and complicated for different types of medical interventions. This type of assistant cancer therapy has been long-term noticed and draw attentions from all scientific disciplines. These advancements include new drug development, optimizing chemotherapeutic schedules, drug combinative strategies, pharmacogenetics [34], individualized antimetastatic therapy [35-37] and pharmaceutical changed [38-42]. Growing bodies of Fib-related assistant cancer therapy studies and applications may help the high quality of clinical cancer trials. According to current studies, there is still shortage of therapeutic efficacy comparison between different types of AC or FA agents in clinics. If we can predict the therapeutic responses among a panel of Fib- or coagulation-related modulators or inhibitors before a clinical cancer trial, we may make correct decisions by utilizing most suitable agents. This type of personalized assistant cancer therapy has a great medical interest. It is the indispensable way to translate these studies from experimental fruits into workable clinical routines (from bench to bedsides).

Conclusion

Fib- or coagulation-related assistant cancer therapies are one of the small numbers of therapeutic interventions that are effective against solid cancer growths and metastasis in clinical trials. Developments of new series of Fib- or coagulation-related modulators or inhibitors specifically to tumor growths and metastasis by the discipline of medicinal chemistry, pharmacology or clinical investigations are extremely necessary. More relevant information must be garnered and taken seriously in order to make a difference in clinical cancer treatments. We wish that these studies

will be beneficial moves for enhancing the therapeutic outcomes in cancer patients. Even great successes can be looked forward.

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