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OLD THEORIES REVISITED ON CANCER ASSISTANT THERAPY

Da-Yong Lu[1] --- Ting-Ren Lu[2] --- Jin-Yu Che[3] --- Hong-Ying Wu[4]

[1]*School of Life Sciences, Shanghai University, Shanghai, PR China*

[2]*College of Science, Shanghai University, Shanghai, PR China*

[3]*Shanghai University, Shanghai, PR China*

[4]*College of Science, Shanghai University, Shanghai, PR China*

ABSTRACT

The causes of cancer deaths are multi-factorials in clinics. Despite the rapid advancement of cancer treatments, many other pathological factors discovered more than half century can also be the targets of cancer therapy. Apart from direct causes from tumor progressions and metastases, many clinical complications or psychiatry factors will more or less speed up these pathogenesis processes of cancer patients, even lost of cancer patients' life. Based on above-mentioned factors, many types of assistant therapies are designed to counter many harmful clinical complications happening in cancer patients. This mini-review offers the panorama of those therapies, addresses and discusses the history and present advancements. Many key factors and efforts and their future impacts are outlined and highlighted.

Keywords: Cancer therapy, Assistant therapy, Individualized cancer therapy, Fibrinogen, Blood thrombosis, Warfarin, Heparin, Traditional Chinese medicine, Antidepressants, Venous thrombosis.

1. INTRODUCTION

The causes of cancer deaths are multi-factorials in clinics. Apart from direct causes from tumor progressions and metastases, other clinical pathogenesis complications will more or less speed up the death of cancer patients. Based on these reasons, many assistant therapies are designed and offered to cancer patients who have some clinical pathogenesis complications or other ill-conditions [1]. Now, many new findings and initiatives have proposed that assistant therapies might ameliorate clinical complicates and receive startling favorable outcome and prolong patients' survival greatly.

2. ANTI-THROMBOSIS THERAPY

2.1. History and Examples

Next to cancer metastasis, the second deadly pathological feature of cancer patients is the venous thromboembolism [2]. For example, cancer patients with obvious venous thromboembolism symptoms have higher-rate of cancer deaths than normal plasma coagulated

cancer patients. It was hypothesized and attempted with assistant therapy of anticoagulants and/or fibrinolytic agents against blood coagulating factors in experiments investigations and clinical trials, such as warfarin, heparin or oxalysine [3].

Disordered coagulation is encountered in up to 90% of cancer patients bearing solid tumors, and 15% of them develop a localized acute or chronic deep thrombosis. The causes of disordered coagulation can be multifactorial events, such as neoplasm metastasis, chemotherapy or hormone therapy (impair the blood vessel walls or promoting coagulate cascade), venous catheters using and immobilization [2]. Furthermore, disordered coagulation can also be caused by multiple blood components, including platelet [4], plasma and tumor matrix of fibrinogen [3, 5, 6] and coagulant component such as thrombin [7, 8]. Most importantly, cancer patients with venous thromboembolism symptoms have been eased by giving assistant therapy of anticoagulants and/or fibrinolytic agents such as warfarin, heparin, tissue plasminogen activator or oxalysine[1, 6] for prolongation of survivals of patients with solid tumors. Many experimental data also supported this scenario.

2.2. Prevention in Surgical Patients

Cancer patients who undergo surgery are at high risk of developing thromboembolic complications. 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. Now, there is a consensus that prophylaxis low-doses of heparin (5000 IU daily for 8-12 h starting 1-2 h before the operation) should be used in patients undergoing solid malignant tissue surgery. A subgroup analysis of cancer patients revealed that low-dose unfractioned heparin is able to reduce DVT from 22% (control) into 9% in solid cancer patients [2].

In non-surgery cancer patients, prophylaxis antithrombosis therapy can be used with a central venous catheter, because central venous catheters will increase the incidence of deep venous thrombosis (DVT) and finally induction of cancer patients' deaths.

2.3. Clinical Choice between Drugs

Anticoagulants and/or fibrinolytic agents are multiple, including warfarin, low-molecular-weight heparin, unfractionated heparin, tissue plasminogen activators, urikinase and clicumarol. Among these anticoagulants and/or fibrinolytic agents, warfarin and low-molecular-weight heparin (LMWH) are especially widely used in clinics.

This type of assistant therapy, nevertheless, might be a double-edged sword. The patients' bleed might happen if the assistant therapy agents are overdosed. The balance between efficacy and toxicity is one of the important factors in clinical trials. Following attentions are needed.

Warfarin is orally given in patients, and it seems to be easily handled. However, there is a great risk of bleeding (haemorrhagic complications) or useless in cancer patient who take warfarin because of inappropriate of blood or plasma concentrations of warfarin in patients' bodies. It is because there is great difference in bioavailability of warfarin in human bodies. The bioavailability

of warfarin can be affected by polymorphism of many drug metabolizing enzymes, majorly human hepatic cytochrome 450 (CYP metabolizing enzymes) [9]. It must be cautious when other drugs are used in a company with warfarin in clinical trials. These pharmacogenetic or pharmacogenomics study needs to be intensified and applied for more drugs. Also warfarin can prolong 5-fluorouracil half-life by potential interaction between warfarin and drugs [10]. Overall, the precise control of the dosage of warfarin for individual cancer patients is relatively difficult. Two ways might solve this problem. One is to constantly detect blood coagulate status of patients (INR level between 1.3 and 1.9). Another way is to utilize pharmacogenomics in deciding warfarin doses [9]. Yet low molecular weight heparin (LMWH) or unfractionated heparin is intravenously or subcutaneously administered and relative easy to accomplish. A lot of patients who fail in warfarin therapy are improved by LMWH or other intravenous injected drugs. Dalteparin (200 IU/Kg daily for 5-7 days) can be administered subcutaneously. It is even easier than heparin.

2.4. Cancer Category that Anti-Thrombosis Therapy Targets

One of important problems is which categories of solid cancer are more suitable for prophylaxis anti-thrombosis therapy. There is no significance improvement of patients' survival in most cancer categories by anti-thrombosis therapy. Only 1/3 of cancer patients showed potential survival benefits by anti-thrombosis therapy [11]. Bobek has reported that patients' survival can be improved greatly in patients with late-staged lung cancer, especially non small cell lung cancer patients by giving anti-thrombosis therapy [12]. Similarly, anti-thrombosis therapy was shown to be effective in patients with breast cancers [2]. Overall, patients with solid tumor categories might be improved by anticoagulant or fibrinolytic agent therapies [3]. But many other articles declare small or moderate survival benefits in clinics. It needs innovative or larger-scale double-blinded investigations for understanding what types of solid cancer or anticoagulant agents might be beneficial to this kind of therapy.

2.5. Combining Anti-Thrombosis Therapy with Cytotoxic or Antimetastatic Anticancer Drugs

Anti-thrombosis therapy is an assistant therapy. It is seldom very successed by using anticoagulants alone. Common anticancer drugs are the mainstream of cancer therapies and they more or less help or inhibit body coagulate system and finally benefit the control of cancer progressions to patients with solid tumors. Conventional first-line anticancer drugs can affect the binding of fibrinogen with tumor cells [8, 13] and in the same times contribute to blood coagulation changes (up or down) in cancer patients [2, 4]. The combinations of anticancer drugs with anticoagulants for patients with solid tumors can expect cooperative effects between them. The theory and mechanism of actions about these researches are urgently needed. Moreover, anti-thrombosis therapy must be combined with anticancer drugs, and its exact mechanism of action is still unresolved. No therapeutic advantage was reported in the group treated with heparin alone [10]. It has been reported a reduced risk of developing liver metastasis in fluorouracil/heparin groups compared to surgery alone or intra-portal infusion of urikinase for 24 h ($P<0.01$) alone.

2.6. Conclusion

Anticoagulants and/or fibrinolytic agents as an assistant therapy for solid cancers can sometimes obviously prolong patients' survival, especially in lung cancer and are promising strategy of cancer therapy, especially in treatment of solid cancer, its metastases, many thrombosis-related complications and deaths. However, some meta-analysis reports showed that many types of solid tumor in clinics improved very little by heparin. It is possible that only small proportions of patients with solid cancer are useful in this way [6]. Previous, anticoagulant prophylaxis in operative ovarian cancer patients has been proved to be cost-effective [14]. So this type of therapy ought to be more commonly used for patients with solid tumors in future. More comprehensive experimental or clinical researches are highly needed, especially on mechanism or theoretical bases.

3. ANTI-DEPRESSANT THERAPY

3.1. Utilization of Antidepressants in Cancer Patients

A lot of people believe cancer is an incurable disease. Some of them frighten to death after hearing the truths of contracting cancer. Mental strength of these cancer patients begins to collapse. The fear of death among cancer patients will speed up the patients' death and reduce the efficacy of following cancer therapy to cancer patients. It has been hypothesized whether antidepressants can be used as an assistant therapy for patients with psychiatry ill-conditioned. If this type of assistant therapy can ease the patients' panic, the longer survival of patients can be foreseeable [15]. But this type of therapies as we predict are only assistant therapies. They do not target tumor cells because tumor cells are caused by genetic abnormality of common cells [16]. Most of times, humans' psychological status is decided by their inherent genetic make-up. Thus pharmacogenomics studies of patients' inherent genetic makeup will be helpful for determining if antidepressants are needed.

3.2. The Side Effects of Antidepressant

Also, antidepressant may have side-effects including suicidal attempts in patients receiving antidepressants, especially in children [17]. Some genetic or molecular factors might affect the intensity of patients' side-effects [18, 19]. It includes updating genetic study systems [20, 21]. Thus, we conclude herein that the psychological assistant therapy is a complicated enterprise and we need greater efforts to systematical study it mechanisms and could find something new.

3.3. Conclusion

Utilization of antidepressants in cancer patients is not new hypothesis. But it is seldom to be attempted in clinics. Lack of successful experimental or clinical outcomes is the possible reasons. But from many theoretical bases, there is high possibility for this type of therapy to become a reality. It is only to find a practical solution. In future, may we try and brainstorm this strategy steps further? Contrary, antidepressants have been found to decrease the efficacy of tamoxifen therapy.

4. TRADITIONAL CHINESE MEDICINE AND OTHER ANCIENT MEDICINES (TCM)

Cancer is a wasting disease and anticancer or antimetastatic drugs many times are very toxic. Drug treated cancer patients become weaker and speed up to deaths only owing to the toxicity of drugs. Many existing ways are proposed and testified for this situation. Both experimental and clinical investigations for advantages or drawback of each possibility must be pursued and implemented in future. Traditional Chinese, Indian or Pakistan medicines (TCM) etc aim to up-balance patients' deleterious physiological conditions and makes patients physically stronger and wades away from worsening physiological conditions caused by disease progression or drug toxicity. TCM is a paradigm of individual therapy survived for long history. Yet it needs the experienced TCM doctors to survey patients' physiological conditions and remedy them after understanding the deficiency of patients' health conditions. The core of TCM treatments rely on balancing between Yin and Yang of different organs and physiological systems [22]. It is a subtle topic and needs long-years experience and comparisons data between TCM and western medicine.

According to traditional Chinese medicine (TCM), human bodies are formed and balanced by fighting between inner upright strength (正气) and outside damaging air (邪气). Individualized therapy of TCM should be based on either strengthening inner upright air (补正气) and preventing or expelling the outsider damaging air (去邪气). In most cancer cases, according to TCM, patients need to strengthen upright air and such a therapy might have better therapeutic benefits than preventing or expelling outside damaging air. Many TCM doctors in China hold such a view.

Treatment of cancer by TCM is a hot topic in modern China. There are many favorable reports for TCM in treatment of cancer patients [23, 24]. In the same times, TCM for cancer has not accumulated enough credit for formally utilized worldwide.

5. ASSISTANT TREATMENT BY WESTERN DRUGS

Cancer is a deteriorating and wasting disease. Cancer patients, especially late stage cancer patients, need more nutrients to keep the body in normal form. This type of assistant therapy also has their western background and gets enough credits for systematic investigations and clinical prescriptions. This type of assistant therapy, such as antioxidants, selenium and nutritional mixtures can be used and seen in the reference [25, 26].

6. CONCLUSIONS

As the accumulation of assistant treatment for cancer patients increases in clinics, more assistant anticancer therapies shall prove useful and more or less to prolong patients' survival. Since drug combination is often effective way to improve patients' survivals [27, 28]. It's time for invitation of larger-scale experimental and clinical studies than ever before. In future, we shall attempt or pay more attentions and efforts on these types of assistant treatment. For assistant therapies, most times, it needs to combine use with anticancer or antimetastatic drugs. Or the therapeutic benefits of assistant therapies will be undermined.

Future trends should be focused on mechanic study of assistant therapy. Furthermore, these studies should help to transform assistant therapy from empirical to science-guided prescriptions for clinical cancer trials. In future, clinical cancer therapy might be changed to individualized cancer therapy (ICT) [29]. Along with other ICT strategies, the integrated therapeutic means should be more innovative, testified and utilized. Let's hope the best.

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8. CONFLICT OF INTERESTS

Authors declare there is no conflict of interests with other institutes and academies.

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