

Cancer Chemotherapy: Time for New Solution

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Commentary:

In the past decades, chemotherapy has become the major therapeutic approaches in several human life-threatening diseases including microbial infections, autoimmune diseases and cancers. Chemotherapy refers to the treatment of disease by the use of chemical substances, such as the antibacterial chemotherapy, autoimmune disease chemotherapy and cancer chemotherapy. Historically, the first modern chemotherapy was used to treat syphilis in 1909 by Paul Ehrlich and his laboratory colleague [1]. They discovered arsphenamine (Salvarsan) for the treatment of syphilis and called it a "magic bullet", thereby initiating the modern concept of chemotherapy. In 1942, Goodman and Gilman began to treat non-Hodgkin's lymphoma with nitrogen mustard [2], this is the beginning of chemotherapy for cancer patients. Nowadays, if without any modifiers before the word "chemotherapy", it usually refers to cancer treatment with one or multiple cytotoxic antineoplastic drugs [3]. The problems of Chemotherapy in cancer treatment are serious adverse effects and drug resistance. Although neoplastic cells are likely to gain genomic mutation to facilitate their rapid and uncontrolled proliferation, they are ultimately homogeneous with normal human cells. Selectivity of anti-neoplastic drugs is therefore hard to achieve in cancer chemotherapy, leading to a series of adverse effects in cancer patients and seriously affect the compliance of the patients. Meanwhile, combination regimens are developed to overcome the multidrug resistance (MDR) of quickly mutated cancer cells, however, the potential unidentified drug-drug interactions may aggravate the adverse effects such as gastrointestinal toxicities and myelosuppression, resulting in limited clinical outcome of chemotherapy. Therefore, it is time for both clinical oncologists and lab investigators to rethink about the solution of cancer treatment.

Existing Drugs Reform: the Form of Drugs, Dosage and Drug Delivery Routes

Oral chemotherapy is likely to lower bioavailability due to existence of first-pass effect, while injection and topical therapy are common ways to avoid the effect. Oral chemotherapeutic agents are unlikely to be effective in treating some particular types of human cancers like hepatocellular carcinoma which have high expression of MDR-related proteins [4], at the same time, metabolism of chemotherapeutic agents by hepatic cytochrome P450 enzymes not only leads to failure of treatment, but also causes terrible toxicity in some cases [5,6]. Transcatheter arterial chemoembolization (TACE) is therefore developed for advanced, non-resectable hepatocellular carcinoma (HCC). By changing the drug delivery route and topical use, TACE was observed to gain optimal therapeutic outcome in treating HCC patients [7]. The success of TACE demonstrated that better outcome may be achievable in terms of changing the dosage form and route of administration in cancer chemotherapy. Advanced knowledge and

practice in medical and pharmaceutical science are feasible to develop topical administration, drug carrier (like liposome), treatment targetable and reasonable chemotherapeutic regimen for cancer therapy.

New Strategy in Chemotherapy: Combination of Other New Medication Therapy

To overcome the adverse effects and resistance of chemotherapeutic agents, we must utilize advanced knowledge in hallmark of cancer which provides useful information for drug discovery and cancer therapy [8]. Although high selective chemotherapeutic agents are hard to obtain, the newly developed targeted therapy drugs can interfere with specific targeted molecules and inhibit tumor growth. Thus, targeted therapy may be a promising cancer treatment for reducing adverse effects and improving quality of life. Unfortunately, like the conventional chemotherapy, resistance still often developed during targeted therapy. Combination of multiple chemotherapy or targeted drugs has been used to fight against drug resistance, the emergence of MDR and the adverse effects from the combination of multiple drugs or target drugs have been challenged for the current cancer treatment. Recently, using nontoxic natural anticancer agents to inhibit cancer development has emerged as a promising option for future cancer treatment [9].

At present, Traditional Chinese medicine (TCM) have been increasingly used as an adjunctive treatment option following surgery, radiation therapy, chemotherapy or targeted therapy for cancer treatment [10]. Chinese medicinal herbs could be a resource of drug discovery which could be developed to be new drugs for alternative cancer treatment. Chinese medicinal herbs could also be developed to be evidence based complementary treatment for chemotherapy cancer. As a drug discovery case, evidence-based arsenic-containing formula was reported [11], but it could be totally different when TCM is used as a complementary with conventional chemotherapy. More and more observations were reported in recent decades which show that using TCM as complementary to conventional chemotherapy could reduce its adverse side effect and improve quality of life of cancer patients. The use of TCM, in many cases, increases patient's tolerance to chemotherapy-induced adverse reactions like myelosuppression and gastrointestinal reactions. A promising case that was found in clinical trials, is PHY906, a herbal product derived from *Scutellaria baicalensis* Decoction (Huang-Qin-Tang in Chinese). A series Phase I/II clinical trials have concluded its efficacy in reducing gastrointestinal toxicity and in enhancing tumor response in cancer patients receiving chemotherapy [12]. In addition to these cases, a lot of Chinese medicinal ingredients or herbal extracts have been proven effective in reducing the side-effects of chemotherapy and reversion resistance, such as codonopsis pilosula, Astragalus, *Scutellaria baicalensis*, ginsenoside, berberine and curcumin [13-16]. These researches have made Chinese medicinal herbs a good candidate for cancer

complementary therapy, although the underlying mechanism of action still needs further investigation.

Conclusion Remark

With the rapid development of novel antitumor agents, the curative effect of chemotherapy in some types of cancer has made significant progress. But overall, for the majority types of tumor the effectiveness of chemotherapy is still limited. For the future, further research should be focused on the development of individualized chemotherapy and novel treatment against chemotherapy resistance. Conventional chemotherapy combine with Chinese medicine to enhance therapeutic effect and reduce adverse effect should be one of complementary and alternative treatment in cancer therapy. Some issues such as combination protocol and herbal-drug interaction should be further studied in laboratory and clinical setting.

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