Overview Article:
Chemoimmunotherapy as a Novel Cancer Therapy

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ABSTRACT

Over the past decade, it was widely accepted that some chemotherapeutic drugs can be combined with immunotherapeutic drugs in treatment of cancer. Chemotherapeutic drugs can induce apoptosis in the tumor cell and at the same time stimulate the immune response. Several reports support the use immunomodulators in treatment of cancers through regulating the immune response and boosting the microenvironments toward T helper (Th1) cells. At the same time these molecule attach to transferrin-Fe^{2+} and circulate in the blood vessels until they find transferin receptors which are highly detected in tumor cells and induce apoptosis in tumor cells.

Introduction

Cancer is the second cause of death worldwide [1]. Common treatments of the cancer are operation, radiation, and chemotherapy. However, many cancers are resistant to treatment or relapse. In addition, physicians must manage a variety of drugs side effects such as activation of intracellular signal nfkB which triggers cancer stem cells with significant impact on patients' quality of life (Unpublished data).

Over the past decade, there has been mainstream acceptance that some chemotherapeutic drugs can be combined with immunotherapeutic agents in animal models. Thus, chemoimmunotherapy can improve the treatment of cancer. What has proven more difficult is knowledge to positive understanding the changing clinical studies. Two drugs, whose effects have been studied (in our laboratory) on animal models, were tested in clinical trials on the patients with breast cancer, invasive ductal carcinoma stage IIB, and chemoresistant patients (end stage). These drugs are tehranloid and shark cartilage. In animal model, we evaluated significant parameters in this regard, including the tumor size, Interferon-Gamma (IFNγ) and Interlukin-4 (IL-4), animal survival, T regulatory cells, and CD4/CD8 ratio in both tehranloid and shark cartilage treated animals. In human trails, we evaluated the CBC level, tumor markers, quality of life and clinical features of the patients.

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The results indicate that shark cartilage could significantly decrease patient's tumor markers, increase quality of life and improve the clinical features of the patients after 60 days of treatment. Shark cartilage could increase IFNγ level, quality of life, and clinical symptoms of the patients, but decrease the level of IL-4 [2].

Cancer Development

Human body smoothly operates all its physiological processes; 60 trillion cells of body are under continuous communication with each other. This communication occurs via two types of molecules; cytokines and cell surface molecules. This physiological process orchestrates the development of the body. Tumor is an abnormal growth of cells coupled with malignant behavior like invasion and metastasis. Many cancers may be related to abnormal immune system function, breakdown in homeostasis, or microflora homeostasis. In this process, both genetic susceptibility and environmental factors and their interactions are implicated [3]. These factors lead to accumulations of genetic mutations in ontogenesis and tumor suppressor genes, which leads to development of cancer, cells with malignant characteristics [4].

Chemotherapeutic Drugs

Anticancer chemotherapeutic drugs have three properties: 1. Damaging the DNA of the tumor cells; 2. Blocking the synthesis of DNA strands to stop the cell replication; and 3. Terminating mitosis duplication of the original cells, i.e. ceasing cell division. Chemotherapy blocks cell division; tumors with high rate of duplication are more sensitive to chemotherapy. Tumors with slower growth rates tend to respond weakly to chemotherapy [5].

Heterogenic tumors may also display varying degrees of sensitivity to chemotherapy, depending on the tumor subclones. Chemotherapy is also used to block the cell growth of some diseases, like autoimmune disorders [6-8]. However they are used at lower doses, to minimize the side effects in treating psoriasis [6] and multiple sclerosis [7]. Cyclophosphamide is sometimes used to treat lupus nephritis, a common symptom of systemic lupus erythematosus [8]. Recently, drugs cocktail has also shown promising results in treatment of cancers.

Immunotherapy

Specific immunotherapy needs several steps to send a death signal for tumor cells. Table 1 presents the required steps to develop specific immunity as well as the steps to delay or inhibit specific immunity.

Nonspecific Immunotherapy

Several reports support the use of immunomodulators in treatment of cancers through regulating the immune response [9] and boosting the microenvironments of immune response toward T helper (Th1) cells. For example, combination of cytokines such as interferon and chemotherapeutic agents will hold a promising therapeutic approach towards the treatment of cancer [10]. More interestingly, these combinations will synergistically potentiate the activity of cytotoxic agents against human tumor cells [10].

Combined Immunotherapy Drugs

Food and Drug Administration (FDA) approved treatment of renal cancer with bevacizumab and interferon-alpha [18] and treatment of melanoma with nivolumab and ipilimumab [19]. Table 2 shows the list of clinical trials of combined immunotherapy.

Combined Chemotherapy and Immunotherapy

Researchers believe that combined anticancer therapies is effective in achieving complete remission and cure for patients with cancer. Chemoimmunotherapy, the combination of immunotherapy and chemotherapy has become the standard treatment for many tumors. Today

Table 1. Default steps in tumor specific immunotherapy

Status	Responses
Antigen/ presentation	Majority of Tumor classified as non-immunogenic, moderate are weak immunogenic (TAA, TATA), minors are immunogenic (TSA such as viral induced tumors)
Priming/ activation/ full activation	Majority of immune cells are inhibited by suppressor molecules.
Homing and traffic/ T cell infiltration	Prognosis is still unclear.
Recognition and killing tumor cells	Responses are weak.

Table 2. Immunotherapy drugs used in clinical trials

Name	Kind of Antibody	Receptor	Tumor
Alemtuzumab	Humanized	CD52	B-cell Chronic Lymphocytic Leukemia (CLL) [11]
Atezolizumab	Humanized	PD-L1	Bladder cancer [12]
Ipilimumab	Human	CTLA4	Metastatic melanoma [13]
Ofatumumab	Human	CD20	Refractory CLL [14]
Nivolumab	Human	PD-1 receptor on activated T cells	[15]
Pembrolizumab	Humanized	Programmed cell Death 1 (PD-1) receptor	Metastatic melanoma [16]
Rituximab	Chimeric	CD20	Non-hodgkin lymphoma [17]

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it is possible to design treatments with immunomodulatory drugs that hold promising therapeutic success particularly in combination with other treatment modalities.

Chemoimmunotherapy

Chemotherapy mostly induce apoptosis. Many of these drugs have a modulatory effect on immune response in dose-dependent way. This mechanism has been demonstrated in animal models with gemcitabine, doxorubicin, cyclophosphamide, and paclitaxel in vivo [30]. Several studies suggest the relevance of this mechanism in humans (Tables 3 and 4). The neoadjuvant therapy of locally advanced breast cancer with paclitaxel results in the accumulation of tumor infiltrating lymphocytes post-treatment, where the extent of T cell infiltration correlates with clinical response [31]. The extent of tumor cell apoptosis with the first paclitaxel treatment predicts the accumulation of Tumor Infiltrating Lymphocyte (TIL) and clinical benefit. For some drugs, including anthracyclines (doxorubicin, daunorubicin, and mitoxantrone) and oxaliplatin, the mechanism underlying immunogenic tumor is not clear [31].

In chemoimmunotherapy, a chemical agent which possesses the antitumor activity, can stimulate patient's immune response. Our proposal is that we can choose a drug which selectively chooses tumor cell through its receptor. For example, tehranloid has high affinity for Fe^{2+} through sesquiterpene lactone bond, also transferrin has high affinity towards Fe^{2+}, so the complex of tehranloid-transferrin Fe^{2+} will be produced. When the patient is injected with tehranloid, it will circulate in the blood vessels and interact with free iron from ferritin and will combine with transferrin.

The complex of tehranloid-transferrin-Fe^{2+} will circulate in the blood vessels until it will find transferrin receptors which is highly detected in tumor cells [32]. At the same time, tehranloid can abrogate T regulatory cell and shift immune response to Th1 [32]. Exact mechanism of tehranloid in shifting immune response is still unclear. Our laboratory focused on the anti-inflammato-

Table 3. Immunotherapeutic drugs in clinical trial research

Immunotherapy	Mechanism	References
Nivolumab+BMS-986016 tumors	Anti-PD1+anti-LAG3 I Solid tumor	Clinical Trials.gov. Identifier:NCT02966548 [20]
Nivolumab+Urelumab	Anti-PD1+anti-4-1BB I/II Solid tumors	Sanmamed MF, et al. [21]
Atezolizumab+MOXR0916	Anti-PDL1+anti-OX40 I Solid tumors	Jeffrey R. [22]
Atezolizumab+GDC-0919	Anti-PDL1+IDO inhibitor I Solid tumors	NCT02471846 clinical trial.gov. Identifier:NCT02471846. [23]
Durvalumab+Tremelimumab	Anti-PDL1+anti-CTLA-4 I/II Melanoma	Antonia S, et al. [24]
Nivolumab+Ipilimumab		Hodi FS, et al. [25]

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Table 4. Immunotherapeutic and chemotherapeutic drugs in clinical trials

Immunotherapy+Chemotherapy	Cancer	References
Pembrolizumab+Cisplatin	Gastric	Clinical Trials. gov. Identifier:NCT02494583 [26]
Pidilizumab+Lenalidomide	Multiple myeloma	Kocoglu M, Badros A. [27]
Idilizumab+Sipuleucel-T+Cyclophosphamide	Prostate	Cheng ML, Fong L. [28]
Nivolumab+Platinum	Lung	Rizvi NL, et al. [29]

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ry property of tehranloid and we noticed that tehranloid significantly inhibits the expression of Nuclear Factor-κB (NF-κB) reporter gene induced by Tumor Necrosis Factor-alpha (TNF-α) (unpublished data).

In another study, we used chemical agent isolated from shark cartilage which has an antiangiogenic property in vitro [33]. This agent injected to animals bearing tumor shows a significant decrease in tumor size, because these molecule has immunomodulatory activity [33-35]. It caused high increase in $CD4^+$ and $CD8^+$ lymphocytes [34] and shifting of cytokine pattern toward T helper 1 (Th1) cells [2, 36].

In human studies on stage IIIB breast cancer treated with shark cartilage, the results indicate that IFNγ and IL-4 levels have reached a stable state after three weeks treatment. Then, significant increase in the level of IFNγ as well as decrease in the level of IL-4 occurred in the patients treated for 12 weeks. The quality of life of the breast cancer patients significantly increased compared to placebo scored by Karnofsky scale [2]. Also we evaluated the effects of shark cartilage on the chemoresistant patients. In this study, we evaluated the patients' CBC, their general health status and did certain biochemical tests.

In this study, we observed a significant decrease in the level of CA15-3 but insignificant improvement in the level of other tumor markers ($P>0.05$). This decrease in the tumor markers may indicate an improvement in the micrometastasis. CA 15-3 was reported to increase in 23% of breast cancer patients, while CEA increase is seen in just 11% of patients [37]. CA 125 in breast cancer patients is indicative of pleural metastases [38]. Also an increased serum carbohydrate antigen, CA19-9, was reported in relapsed ductal breast carcinoma [39]. Our results indicate an improvement in the clinical condition of the patients after treatment with shark cartilage. The results indicate an improvement in the secondary tumor size and metastasis in the body. The patients were satisfied with this protocol of treatment.

We used Karnofsky performance scale in determining outcomes and risk in geriatric outpatients. Our results exhibit an improvement in the patients' quality of life after treatment with shark cartilage [40]. Recent drugs are shown to induce apoptotic activity toward cancer cell as well as stimulate the immune response IFNγ and reduce the T regulatory inside tumor in animal model and nowadays are used in human (phase I). For example, artemisinin, as the active component of Artemisia annua, isolated in 1972 [41] and its structure, being unique among anti-malarial drugs, was determined in 1979 [41]. Artemisinin is a sesquiterpene lactone containing an endoperoxide bridge essential for its activity. Dihydroartemisinin is by no means toxic, indicating that the endoperoxide bridge contributes significantly to cytotoxicity [42]. Because of its profound anti- malarial activity, this compound has been of special biological interest.

Ethical Considerations

Compliance with ethical guidelines

Ethical guidelines permission was taken from University of Shahed and National Institute of Cancer Research, Imam Khomani Hospital.

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Conflict of interest

The authors declared no conflict of interest.

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