

# 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<sup>2+</sup> and circulate in the blood vessels until they find transferrin 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of intracellular signal nfκB which triggers cancer stem cells with significant impact on patients' quality of life (Unpublished data).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 IFN $\gamma$  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, tehranoid has high affinity for Fe<sup>2+</sup> through sesquiterpene lactone bond, also transferrin has high affinity towards Fe<sup>2+</sup>, so the complex of tehranoid-transferrin Fe<sup>2+</sup> will be produced. When the patient is injected with tehranoid, it will circulate in the blood vessels and interact with free iron from ferritin and will combine with transferrin.

The complex of tehranoid-transferrin-Fe<sup>2+</sup> will circulate in the blood vessels until it will find transferrin receptors which is highly detected in tumor cells [32]. At the same time, tehranoid can abrogate T regulatory cell and shift immune response to Th1 [32]. Exact mechanism of tehranoid 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 tehranoid and we noticed that tehranoid significantly inhibits the expression of Nuclear Factor- $\kappa$ B (NF- $\kappa$ B) reporter gene induced by Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) (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<sup>+</sup> and CD8<sup>+</sup> 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 IFN $\gamma$  and IL-4 levels have reached a stable state after three weeks treatment. Then, significant increase in the level of IFN $\gamma$  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 IFN $\gamma$  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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References

- [1] World Health Organization. Cancer. Geneva: World Health Organization; 2018.
- [2] Shahrokhi S, Zuhair MH, Mohagheghi MA, Ghazanfari T, Askarian Sh, Sheikhan A, et al. [The effect of oral consumption of shark cartilage on the cellular immune responses of cancer patients (Persian)]. *Yafteh*. 2006; 8(3):15-21.
- [3] Nickels S, Truong T, Hein R, Stevens K, Buck K, Behrens S, et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. *PLoS*. 2013; 9(3):e1003284. [DOI:10.1371/journal.pgen.1003284]
- [4] Payne SR, Kemp CJ. Tumor suppressor genetics. *Carcinogenesis*. 2005; 26(12):2031-45. [DOI:10.1093/carcin/bgi223] [PMID]
- [5] Chabncr BA. The role of drugs in cancer treatment. In: Chabner BA, editor. *Pharmacologie Principles of Cancer Treatment*. Philadelphia: Saunders; 1982.
- [6] McDonald CJ. The uses of systemic chemotherapeutic agents in psoriasis. *Pharmacology & Therapeutics*. 1981; 14(1):1-24. [DOI:10.1016/0163-7258(81)90008-5]
- [7] Kieseier BC, Jeffery DR. Chemotherapeutics in the treatment of multiple sclerosis. *Therapeutic Advances in Neurological Disorders*. 2010; 3(5):277-91. [DOI:10.1177/1756285610379885]
- [8] Traynor AE, Schroeder J, Rosa RM, Cheng D, Stefka J, Mujais S, et al. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: A phase I study. *Lancet*. 2000; 356(9231):701-7. [DOI:10.1016/S0140-6736(00)02627-1]
- [9] Escudier B, Pluzanska A, Koralewski P, Ravaud A, Braarda S, Szczylak C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. *The Lancet*. 2007; 370(9605):2103-11. [DOI:10.1016/S0140-6736(07)61904-7]
- [10] Larkin J. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England Journal of Medicine*. 2015; 373(13):1270-1. [DOI:10.1056/NEJMoa1504030] [PMID] [PMCID]
- [11] Robak T. Alemtuzumab for B-cell chronic lymphocytic leukemia. *Expert Review of Anticancer Therapy*. 2008; 8(7):1033-51. [DOI:10.1586/14737140.8.7.1033]
- [12] ClinicalTrials.gov. A phase II Study of atezolizumab in combination with cisplatin+gemcitabine before surgery to remove the bladder cancer. 2018; Identifier: NCT02989584.
- [13] Savoia P, Astrua C, Fava P. Ipilimumab (Anti-Ctla-4 Mab) in the treatment of metastatic melanoma: Effectiveness and toxicity management. *Human Vaccines & Immunotherapeutics*. 2016; 12(5):1092-101. [DOI:10.1080/21645515.2015.1129478] [PMID] [PMCID]
- [14] Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, et al. Ofatumumab as single-agent cd20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology*. 2010; 28(10):1749-55. [DOI:10.1200/jco.2009.25.3187]
- [15] Guo L, Zhang H, Chen B. Nivolumab as Programmed Death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. *Journal of Cancer*. 2017; 8(3):410-6. [DOI:10.7150/jca.17144]
- [16] Sui X, Ma J, Han W, Wang X, Fang Y, Li D, et al. The anticancer immune response of anti-PD-1/PD-L1 and the genetic determinants of response to anti-PD-1/PD-L1 antibodies in cancer patients. *Oncotarget*. 2015; 6(23): 19393-404. [DOI:10.18632/oncotarget.5107]
- [17] Dotan E, Aggarwal C, Smith MR. Impact of rituximab (Rituxan) on the treatment of B-cell Non-hodgkin's lymphoma. *Journal of Orthopaedic & Sports Physical Therapy*. 2010; 35(3):148-57. [PMID] [PMCID]
- [18] Summers J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: Bevacizumab plus interferon for advanced renal cell carcinoma. *The Oncologist*. 2010; 15(1):104-11. [DOI:10.1634/theoncologist.2009-0250]
- [19] Hazarika M, Chuk MK, Theoret MR, Mushti S, He K, Weis SL, et al. U.S. FDA approval summary: Nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. *Clinical Cancer Research*. 2017; 23(14):3484-8. [DOI:10.1158/1078-0432.CCR-16-0712]
- [20] ClinicalTrials.gov. Safety study of anti-LAG-3 with and without anti-PD-1 in the treatment of solid tumors. 2018; Identifier: NCT02966548.
- [21] Sanmamed MF, Rodriguez I, Oñate C, Azpilikueta A, Rodriguez-Ruiz ME, Morales-Kastresana A, et al. Abstract 261: Nivolumab and urelumab enhance antitumor activity of human T lymphocytes engrafted in Rag2-/-IL2R $\gamma$  null immunodeficient mice. *Cancer Research*. 2015; 75(15 Suppl):261. [DOI:10.1158/0008-5472.CAN-14-3510] [PMID]
- [22] Jeffrey R. Infante Combining Atezolizumab With OX40 Agonist Shows Promise in Solid Tumors Community Practice Connections™. Paper presented at: 12<sup>th</sup> Annual International Symposium on Melanoma and Other Cutaneous Malignancies. 20 February 2016; Miami, USA.
- [23] ClinicalTrials.gov. A study of GDC-0919 and atezolizumab combination treatment in participants with locally advanced or metastatic solid tumors. 2018; Identifier: NCT02471846.
- [24] Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumor activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. *The Lancet Oncology*. 2016; 17(3):299-308. [DOI:10.1016/S1470-2045(15)00544-6.] [PMID] [PMCID]
- [25] Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *The Lancet Oncology*. 2016; 17(11):1558-68. [DOI:10.1016/s1470-2045(16)30366-7]
- [26] ClinicalTrials.gov. Study of pembrolizumab (MK-3475) as first-line Monotherapy and combination therapy for treatment of advanced gastric or gastroesophageal junction adenocarcinoma (MK-3475-062/KEYNOTE-062); 2015. Identifier: NCT02494583.
- [27] Kocoglu M, Badros A. The role of immunotherapy in multiple myeloma. *Pharmaceuticals*. 2016; 9(1):3. [DOI:10.3390/ph9010003]

- [28] Cheng ML, Fong L. Beyond sipuleucel-T: Immune approaches to treating prostate cancer. *Current Treatment Options in Oncology*. 2014; 15(1):115–26. [DOI:10.1007/s11864-013-0267-z]
- [29] Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghaei H, Gettinger S, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. *Journal of Clinical Oncology*. 2016; 34(25):2969–79. [DOI:10.1200/jco.2016.66.9861]
- [30] Shikanov S, Shikanov A, Gofrit O, Nyska A, Corn B, Domb AJ. Intratumoral delivery of paclitaxel for treatment of orthotopic prostate cancer. *Journal of Pharmaceutical Sciences*. 2009; 98(3):1005–14. [DOI:10.1002/jps.21492]
- [31] Hortobágyi GN. Anthracyclines in the treatment of cancer. *Drugs*. 1997; 54(4):1-7. [DOI:10.2165/00003495-199700544-00003] [PMID]
- [32] Noori S, Taghikhani M, Hassan ZM, Allameha A, Mostafaei A. Tehranolide molecule modulates the immune response, reduce regulatory T cell and inhibits tumor growth in vivo. *Molecular Immunology*. 2010; 47(7-8):1579–84. [DOI:10.1016/j.molimm.2010.01.007]
- [33] Hassan ZM, Feyzi R, Sheikhan A, Bargahi A, Mostafaie A, Mansouri K, et al. Low molecular weight fraction of shark cartilage can modulate immune responses and abolish angiogenesis. *International Immunopharmacology*. 2005; 5(6):961–70. [DOI:10.1016/j.intimp.2005.01.006] [PMID]
- [34] Safari E, Hassan ZM, Moazzeni SM. Shark cartilage 14 kDa protein as a dendritic cells activator. *Immunopharmacology and Immunotoxicology*. 2015; 37(2):165-70. [DOI:10.3109/08923973.2015.1006370]
- [35] Feyzi R, Hassan ZM, Mostafaie A. Modulation of CD4+ and CD8+ tumor infiltrating lymphocytes by a fraction isolated from shark cartilage: Shark cartilage modulates anti-tumor immunity. *International Immunopharmacology*. 2003; 3(7):921–6. [DOI:10.1016/S1567-5769(02)00255-2]
- [36] Shahrokhi S, Zuhair MH, Mohagheghi MA, Ghazanfari T, Ebtekar M. Shark cartilage modulates immune responses in stage III breast cancer patients. *International Journal of Hematology-Oncology and Stem Cell Research*. 2009; 3(3):21-8.
- [37] O'Dwyer PJ, Duffy MJ, O'Sullivan F, McDermott E, Losty P, O'Higgins NJ. CEA and CA 15-3 in primary and recurrent breast cancer. *World Journal of Surgery*. 1990; 14(5):562–5. [DOI:10.1007/BF01658788] [PMID]
- [38] Jäger W, Kissing A, Cilaci S, Melsheimer R, Lang N. Is an increase in CA 125 in breast cancer patients an indicator of pleural metastases? *British Journal of Cancer*. 1994; 70(3):493–5. [DOI:10.1038/bjc.1994.333] [PMID] [PMCID]
- [39] Papantoniou V, Tsiouris S, Koutsikos J, Ptohis N, Lazaris D, Zerva C. Increased serum carbohydrate antigen 19-9 in relapsed ductal breast carcinoma. *Hellenic Journal of Nuclear Medicine*. 2006; 9(1):36-8. [PMID]
- [40] Sarraf A, Ghazanfari T, Gharib B, Sedaghtsayar S, Shirvanian F, Faghizadeh S, et al. Evaluation shark cartilage effect on Treated Invasive Ductal Carcinoma Patients (Unpublished).
- [41] Crespo-Ortiz MP, Wei MQ. Antitumor Activity of Artemisinin and Its Derivatives: From a Well-Known Antimalarial Agent to a Potential Anticancer Drug. *Journal of Biomedicine and Biotechnology*. 2012; 2012:1–18. [DOI:10.1155/2012/247597]
- [42] Noori S, Hassan ZM. Dihydroartemisinin shift the immune response towards Th1, inhibit the tumor growth in vitro and in vivo. *Cellular Immunology*. 2011; 271(1):67–72. [DOI:10.1016/j.cellimm.2011.06.008] [PMID]