Leukemia Research 35 (2011) 1136–1142

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Invited review

Combining cytokine-induced killer cells with vaccination in cancer immunotherapy: More than one plus one?

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ARTICLE INFO

Article history:
Received 13 December 2010
Received in revised form 8 March 2011
Accepted 9 May 2011
Available online 8 June 2011

Keywords:
Immunotherapy
CIK cells
Dendritic cells
Vaccination
Clinical trials
Cancer

ABSTRACT

The immune system can be harnessed to fight cancer by active (stimulating the patient's intrinsic immune response to cancer) and by passive (transfer of active humoral or cellular immunity) immunotherapy. While for each strategy proof-of-principle was provided, clinical benefit was limited likely due to malfunction of lymphocytes. Increasing knowledge of both the mechanism of vaccination through dendritic cells (DCs) and the potency of a subset of natural killer T lymphocytes termed cytokine-induced killer (CIK) cells led to new strategies through combining adoptive and passive immunotherapy. This review summarizes most recent clinical trials indicating that CIK cells can substantially enhance the effect of tumor vaccines and discusses the potential therapeutic benefit in the long-term control of tumor progression.

Contents

1. Introduction

Many patients with advanced malignant disease cannot be cured by standard cancer therapy. Surgery, radiation, and chemotherapy have multiple side effects and often fail to completely remove the tumor load leaving small lesions and metastatic cells which may cause relapse of the disease even after years. Immunotherapy is a promising treatment option for various cancers with the aim to establish long-lasting tumor control. The strategy takes advantage of the immune system to recognize and eliminate tumor cells by stimulating and redirecting the cellular immune response in cancer patients.Various subsets of effector T cells with cytotoxic capacities were explored in the anti-tumor therapy over the last years. A subset of natural killer T lymphocytes called cytokine-induced killer (CIK) cells provided encouraging results in clinical studies in both autologous and allogeneic context. CIK cells have a profound capacity to cytolytically eliminate tumor cells. CIK cells are predominantly $CD3^+CD56^+$ type II natural killer T-cells [1] and are generated *ex vivo* by incubation of peripheral blood lymphocytes with an agonistic anti-CD3 monoclonal antibody, interleukin (IL)-2, IL-1-beta and interferon (IFN)-gamma. Compared to lymphokine-activated killer (LAK) cells, CIK cells exhibit enhanced cytotoxic activity [2,3], a higher proliferation rate and remarkably low toxicity (Table 1). The improved anti-tumor activity of CIK cells is mainly attributed to the pronounced proliferation rate leading to an increase in total lytic units [4].

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doi:10.1016/j.leukres.2011.05.005

Table 1
Animal models using CIK cells.

Reference	Animal tumor model	Effect of CIK cell application
Shi et al. (2010) [34] Anti-tumor activity of safflower polysaccharide (SPS) and effect on cytotoxicity of CTL cells, NK cells of T739 lung cancer in mice	LA 795 lung cancer in mice	Reduction of tumor volume
Kim et al. (2009) [35] Inhibition of human cervical carcinoma growth by cytokine-induced killer cells in nude mouse xenograft model	KB-3-1 human cervical cancer in nude mouse	Inhibited tumor growth
Kim et al. (2009) [36] Antitumor activity of cytokine-induced killer cells in nude mouse xenograft models	U-87 MG human glioma in nude mouse	Inhibited tumor growth
Wang et al. (2008) [37] Experimental study on the treatment of intracerebral glioma xenograft with human cytokine-induced killer cells	U251 human glioma in nude mice	Inhibition of glioma growth Strong suppressive effect on glioma growth
Chang et al. (2008) [38] Specific immune cell therapy against ovarian cancer in vivo and *in vitro*	SK-OV-3 human ovarian cancer in SCID mice	Tumor weight was lighter
Kim et al. (2007) [39] Anti-tumor activity of *ex vivo* expanded cytokine-induced killer cells against human hepatocellular carcinoma	SNU-354 human HCC in irradiated nude mice	Inhibited tumor growth
Kim et al. (2007) [40] Antitumour activity of cytokine-induced killer cells against human lung cancer	NCI-H460 human lung cancer in nude mice	Inhibited tumor growth
Kim et al. (2007) [41] Inhibition of human ovarian tumor growth by cytokine-induced killer cells	SK-OV-3 human ovarian cancer in nude mice	inhibited tumor growth
Yang et al. (2006) [42] Antitumor effects of cocultured dendritic cells and cytokine-induced killer cells on lung cancer *in vitro* and in vivo	A549 lung cancer in nude mice	Inhibitory effects on the growth of transplanted tumor cells
Shi et al. (2004) [43] Growth inhibition of human hepatocellular carcinoma xenograft in nude mice by combined treatment with human cytokine-induced killer cells and chemotherapy	BEL-7402 human HCC in nude mice	Higher survival rate Tumor grew slowly
Ge et al. (2004) [44] Coculture of dendritic cell with cytokine-induced killer results in a significant increase in cytotoxic activity of CIK to tumor cells *in vitro* and in vivo	NB4 human leukemia in nude mice	Inhibition of the tumor growth Increased tumor free survival rate
Wang et al. (2002) [45] Antitumor activities of human autologous cytokine-induced killer (CIK) cells against hepatocellular carcinoma cells *in vitro* and in vivo	BEL-7402 human HCC in nude mice	Inhibited tumor growth

While passive immunotherapy by adoptive transfer of T cells can reject established tumors, such passive immunotherapy is unlikely to control tumor outgrowth in the long-term. Active immunotherapy, in contrast, using tumor-specific vaccines has the potential to induce tumor-specific effector and memory T cells. Vaccines are presented to the immune cells by dendritic cells (DCs), the major professional antigen presenting cells, which induce, regulate and maintain T cell response. DCs capture and process antigens including tumor-associated antigens, may express lymphocyte costimulatory molecules, and secrete cytokines to initiate the cellular and humoral immune response [5]. Coculture of CIK cells led to a significant increase of DC-specific, costimulatory, and antigen-presenting molecules in DC cultures. In addition, coculture resulted in a dramatically increase of IL-12 secretion by DCs and to a significant increase in cytotoxic activity of CIK cells towards carcinoma cells. Blockage of IL-12 uptake decreased the cytolytic activity of CIK cells. Cytokine secretion was shown to be important for activation of CIK cells, and also cellular interactions between DCs and effector cells caused a higher cytolytic capacity. Interactions between DCs and CIK cells caused changes in the surface molecule expression of both populations, led to an increase of IL-12 secretion, and rendered an improved cytotoxic activity. The natural killer T cell subpopulation seems to be responsible for this effect [5]. Different DC cell subsets, the major being myeloid and plasmacytoid DCs, mediate different types of adaptive immune responses. Approaches to DC-based immune interventions include (i) application of antigen with or without adjuvant that target resident DCs randomly in the draining lymph node, (ii) *ex vivo* generated tumor antigen-loaded DCs re-administered to the patient, or (iii) in vivo DC targeting with anti-CD antibodies fused with the antigen. Recent trials indicate that cancer patients treated with *ex vivo* generated DCs as therapeutic vaccines can experience an anti-tumor response. However, the fraction of patients with durable objective tumor regression is low. The most common outcome is the demonstration of expanded antigen-specific response in the absence of clinical response [6].

DC cells can be propagated *ex vivo* under various culture conditions which, however, impact the phenotypical and functional properties of dendritic cells and thereby the elicited immune response [7]. For adoptive transfer in clinical trials, DCs from cancer patients are pulsed with tumor antigens *in vitro* and subsequently transferred to the hosts to enhance the immune response against tumor targets, particularly mediated by infiltrating T cells [8]. Several clinical trials have shown proof-of-principle in several tumor types.

1.1. Combining CIK cells and DC vaccination

Each strategy, DC vaccination and adoptive CIK cell transfer, provided proof-of-principle in trials with respect to therapeutic immunity being elicited leading to clinical responses. However, clinical benefit in long-term is harmed due to impairment of lymphocyte function due to e.g. aberrant expression of NKG2DLs by tumor cells or altered hematopoiesis in many cancer patients. While *ex vivo* antigen loading of dendritic cells from cancer patients helps to bypass the dysfunction of endogenous DCs existing in many cancer patients, adoptive transfer of highly activated CIK cells is thought to improve the effector arm in executing tumor cell lysis. A number of *in vitro* evidences support the assumption that