Cancer Cell International

Poster presentation

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Development, monitoring and first immunological results of a phase I/II vaccination trial using genetically modified allogeneic breast cancer cells

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from Association for Immunotherapy of Cancer: Cancer Immunotherapy – 2nd Annual Meeting
Mainz, Germany, 6–7 May 2004

Published: 1 July 2004

Received: 28 April 2004

Cancer Cell International 2004, **4**(Suppl 1):S38

This article is available from: http://www.cancerci.com/content/4/S1/S38

The rational behind the use of allogeneic tumor cell lines as therapeutical vaccines is that multiple antigens common to both, the immunizing cell line and the patient's tumor are presented by shared human leukocyte antigen (HLA) molecules. The cell line "KS" was established from a malignant effusion of a breast cancer patient and found to express an array of ubiquitous tumor associated antigens (TAA) such as MUC-1, CEA, SSX-2, and members of the MAGE-family. As a result of interferon(IFN)-γ stimulation KS cells express high levels of HLA molecules, which probably present multiple peptide ligands for polyclonal T cell activation. This KS cell line was genetically modified to express CD80 providing costimulatory signals to T lymphocytes, and further transfected to overexpress Her-2/neu in order to avail a well characterized TAA as a marker for immunodiagnostic. *In vitro* studies demonstrated: a) KS24.22 transfectants can induce allospecific responses through direct priming; b) activate cytotoxic T cells (CTL) and T_H cells; c) stimulate antigen-specific HLA-A*02-restricted CTL after transfection with viral antigens; and d) present TAA epitopes restricted by HLA-A*02. These results supported the realisation of a phase-I/II clinical trial, where KS24.22 cells are used to vaccinate patients with breast cancer. KS24.22 were expanded under GMP conditions and safety testing was done following FDA criteria. The primary objectives of the study are toxicity and feasibility. To correlate vaccine-induced immune responses with clinical responses we evaluated KS24.22-associated and TAA-specific T cells with a combination of molecular and cellular immunodiagnostic tests (qRT-PCR, ELISpot). Eligibility criteria included the following: (1) measurable metastatic breast cancer; (2) patient already received either anthracyclin- or taxan-based chemotherapy; (3) HLA-A*0201-positivity; (4) *in vitro* activation of patient's T cells by mitogen antibodies and KS24.22 vaccine cells; (5) written informed consent. Patients were excluded for following reasons: (1) immunosuppressive or autoimmune diseases; (2) acute or systemic infections; (3) chemotherapy or radiotherapy within 4 weeks; (4) antibodies, cytokines, or other immune therapies within 6 weeks. After irradiation, 10^7 cells were injected i.d. four times at 2-week intervals and four times monthly. The protocol was approved by the the local ethic-committees, the Paul-Ehrlich-Institut and the Committee for Somatic Genetherapy of the Deutsche Ärztekammer.

So far, 10 patients were included in this study receiving together more then 70 vaccinations. Vaccinations showed only minor side effects like flulike symptoms and injection site reactions. Here, the immunohistochemical analysis of biopsies showed infammatory cell infiltration consisting of macrophages, dendritic cells and predominantly $CD4^+$ T cells. Three patients had to discontinue

therapy because of progression. Disease stabilisation was observed in seven patients. Of these, postvaccination PBMCs showed increasing KS24.22-reactive T cell responses detected by quantifying antigen-induced IFN-γ-mRNA. Two patients clearly developed HLA-A*02-restricted, Her-2/neu-specific $CD8^+$ T cells alongside with KS24.22-related alloresponses. CEA- and MAGE-1-specific $CD8^+$ T cells could be detected as well.

In summary, this immunization strategy proved to be safe and feasible, and induced TAA-specific immune responses. However, no objective tumor regressions were observed so far. The qRT-PCR method proved to be highly sensitive and can be used to perform an "immunologic staging" under vaccination.