Autologous Immune Enhancement Therapy for Cancer - Our experience since 2004

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Abstract

Introduction:

Cancer, the major killer disease of the century requires a multi-pronged approach and among the latest modalities of treatments, Immunotherapy occupies a promising role. Immunotherapy for cancer was first started to be practised in the NIH and cell based immunotherapies for various solid tumours and haematological malignancies. [1-4] There are several literatures from various countries on the successful application of cell based Immunotherapies for various solid tumours and haematological malignancies. [3-8] Our team's association with immune cells started when I was working on RNA transcriptome analysis to understand the immune system in HIV carriers which in turn required in vitro expansion of human Natural Killer (NK) cells. [9] This led to the customization of protocols which has resulted in successful in vitro expansion, activation of NK cells and T cells for Immunotherapy. The purpose of Biotherapy institute of Japan (BIJ) is to support research and clinical application of immune cells like NK cells, γδT cells, αβT cells, Cytotoxic T lymphocytes (CTL) and Dendritic cells (DC) for application as Autologous Immune Enhancement Therapy (AIET) to fight against cancer. AIET using NK cells, CTLs, DCs etc have been administered for more than 5000 patients since 2004 till date by BIJ.

Principle of AIET:

For AIET using NK cells, the process involves separation of lymphocytes from the peripheral blood of the patient followed by selective NK cell expansion using the expansion kit (BINKIT, BIJ, JAPAN) without feeder layers and then infusion of the expanded-activated NK cells. [10,11] As reports suggest that the activity of peripheral blood NK cells are lower in cancer patients compared to normal individuals [12] and as in vitro expansion of NK cells increases the cytotoxic ability 5 to 10 fold, [13] the NK cells are expanded in vivo and then infused to the patient in AIET.

We are also working on combination immunotherapy using NK cells and CTLs and also NK cells and peptide pulsed DCs. The principle behind combining NK cells and CTLs is a dual advantage approach combining the innate immune system and adaptive immune system wherein the CTLs will kill the MHC expressing cancer cells while NK cells will kill the MHC non-expressing cancer cells also. [10] In case of NK cells and DCs, DCs will in turn activate the CTLs thereby giving rise to the dual advantage mentioned above. We have recently suggested that the AIET using expanded NK cells, particularly in combination with monoclonal antibody drugs, may be very useful tool for cancer immunotherapy. [14]

Our experience:

In our studies in NOG SCID mice, activated NK cells were shown to reduce the size of breast cancer cells (MDA-MB231) [15] and the volume of ascites also inhibiting lung metastasis of pleural effusion lymphoma (PEL) cells. [16] In a primary lung adenocarcinoma patient where AIET was administered in combination with Hyperthermia, the CEA values decreased from 4.8 ng/ml to 1.6 ng/ml, the SLX decreased from 30 U/ml to 27 U/ml, the IAP reduced from 300 μg/ml to 221 μg/ml along with resolution of the lung lesions in four months. A 55 year old woman treated for invasive ductal carcinoma of breast presented with metastasis to the lungs. She was then treated with trastuzumab in combination with multiple injections of activated natural killer (NK) cells (at two week intervals) following which the tumor markers decreased. Progression free survival was 10 months. [17] Fifty-two patients with advanced cancers in organs like lung, breast, colon, prostate, liver, kidney, ovary etc, refractory to conventional therapy when treated with a combination of hyperthermia and NK cell-and CTL-based immune cell therapy with low-dose chemotherapy, in 18 of 52 patients, objective responses was observed including one complete response (CR) and 17 partial responses (PR) evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Sixteen patients had stable disease (SD), whereas 18 had progressive disease (PD). Disease control rate was 66% including CR, PR and SD. After treatment for six months, the objective responses and disease control rate were 25% and 52%, respectively. There were no adverse effects in any of these patients. [17]
Conclusion:

Cancer has to be tackled with a multipronged approach and combining NK cell and CTL cell based AIET with conventional modalities of treatments such as Surgery, Chemotherapy and Radiotherapy as well as other modalities like Hyperthermia, Proton Beam therapy and low dose chemotherapy is effective even in advanced cancers which are refractory to conventional therapeutic modalities.

References: