Papers submitted on the II-nd Spring Seminar on Treatment Planning in Radiotherapy in Poznań, Poland 20-21 may 1996

GENE THERAPY OF CANCER

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Gene therapy belongs to the most rapidly developing fields of modern medicine what is closely related to the achievements in genetic engineering particularly to the development of the DNA (gene) transfer into eucariotic cells technology. During last fiver years 120 clinical protocols of human gene therapy have been designed which involve about 600 patients. About half of the protocols are currently in the phase I or II clinical trials. In Europe 6 out of 15 approved clinical protocols including one in Poland are currently curried out. Majority of protocols (60%) concern neoplastic diseases, 25% hereditary genetic disorders, 10% AIDS and remaining 5% rheumatic or vascular diseases.

Gene therapy may be defined as an alteration of the cell phenotype by insertion of the "correct" or removal of "incorrect" genetic information or modification of normal cell by introduction of a new information in order to control or threat the disease. Cells may be genetically modified ex vivo (cellular gene therapy) or in vivo (gene therapy).

The basis of gene therapy form vectors introducing DNA into target cells. Two types of vectors, viral and non-viral vectors are currently applied in human trails. Non-viral vectors are cationic lyposomes. Viral vectors are based on retroviruses, adenoviruses, adeno-associated viruses and herpesviruses. In two clinical protocols "naked" DNA is injected into cells. In two/third of protocols retroviral vectors are employed.

Number of hereditary disorders is caused by a single gene defect what leads to the malformation of the particular metabolic pathway. In such cases therapy would be based on the transfer of functional copy of the gene into defective cell. However, highest expectations of the development of the gene therapy are related to the neoplastic diseases. Cancer therapy clinical protocols being in trial are based on 5 strategies: (i) genetic cellular cancer vaccines; (ii) introduction of major histocompability complex (MHC) antigens directly into tumor cells in situ; (iii) introduction of suicide genes into tumor cells in situ and activation of suicide mechanisms; (iv) introduction into tumor cells of suppressor genes and/or anti-oncogenes and blocking of oncogenes expression; (v) introduction of multidrug resistance genes (MDR) into bone marrow cells in order to protect them from high dose chemotherapy.

The larger number of cancer gene therapy clinical protocols deals with cancer cellular genetic vaccines. Strategy of these vaccines is to deliver locally together with cancer cells factors (most frequently cytokines) which will induce anti-cancer specific and non specific responses by enhancing presentation of tumor antigens or by providing costimulatory signals for immune system. Cytokines might be provided by transfer of their genes into autologous tumor cells, allogeneic cell lines or fibroblasts which will be then mixed with autologous tumor cells. Autologous cellular genetic vaccines are prepared by ex vivo transfer of cytokine genes into patient's own tumor cells cultured in vitro, which are then irradiated and subcutaneously injected back to the patient. Basis of allogeneic vaccines form cancer established cell lines which are transduced with genes coding particular cytokine or other factors. In the case of melanoma HLA-A1 and HLA-A2 positive cell lines which express MAGE and MART antigens are selected, . Allogeneic vaccines in certain circumstances, such as problems with obtaining cancer tissue from the patient, might be alternative to autologous vaccines. In general preparation of autologous vaccines is difficult while allogeneic vaccines are believed to be less effective. Accordingly, efforts are undertaken to develop mixed vaccines. They comprise of autologous tumor cells which are isolated from cancer tissue and frozen without genetic modification and cells producing cytokines. Autologous fibroblasts or allogeneic cell

lines (as developed in our Department) modified to secrete cytokines may be employed.

Interleukin 6 (IL-6) displays its activity through a membrane specific receptor composed of two subunits a (gp80, CD126) and ß (gp130, CD130)[Mackiewicz et aleds, 1995]. IL-6 binds to subunit a (without transducing a signal) and then attracts two molecules of subunit ß, what leads to signal transduction. Soluble form of gp80 (sIL-6Ra) acts agonistically with IL-6. IL-6/sIL-6Ra complex displays different biological activities than IL-6 alone since it may activate cells which express only gp130, while IL-6 requires both subunits. Transfer of IL-6 and sIL-6Ra genes into murine melanoma cells results in the inhibition of tumor growth and metastases formation. Immunization of mice with IL-6/sIL-6Ra transduced melanoma cells induced long lasting, specific anti-melanoma immunity. Based on the preclinical studies clinical protocol for Immunogene therapy of human melanoma was designed in our Department [Mackiewicz et al, 1995]. In January 1995 phase I clinical trial was initiated. Until now 8 patients with IV clinical degree of melanoma received genetic vaccine. 2.5 x 10^7 autologous cells were mixed with the same mount of allogeneic cells modified to secrete IL-6 and sIL-6R and injected to patients according to following schedule: 4 injections in two weeks intervals, 3 injections in one month intervals and 3 injections in
two months intervals. During therapy no toxic effects were observed. Induction of specific and non-specific anti-melanoma
response was observed. Currently the trial enters phase II. Optimalization of doses and immunization schedule as well as verification of patients eligibility will be carried out. Moreover, clinical effects of applied therapy will be monitored.

REFERENCE

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