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Case Report

Glioblastoma and Successful Cancer Immuno-Gene Therapy

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Abstract

Targeting the Insulin-like Growth Factor1 (IGF-I) system present in a brain tumor-glioblastoma multiforme, GM, has emerged as a useful method to reduce malignant development. Using anti-gene anti-IGF-I technology (antisense, AS and triple helix, TH), applied in glioma cell culture established from GM biopsies induces the expression of B7 and MHC-I antigens in transfected cells (immunogenic cell tumor vaccines). After subcutaneous injection of vaccines, an immune response mediated by T CD8+ and T CD28+ lymphocytes was initiated, and followed by tumor regression. The GM patients treated classically by surgery and radiotherapy, while followed by immuno-gene therapy, have reached 21 - 24 months of median survival.

Keywords: *Glioblastoma; Immuno-Gene Therapy; Anti-Gene IGFI*

Starting in 2016, cancer immunotherapy or immuno-gene therapy became a principal complementary therapy in the United States with the program "The Cancer Moonshot" overseen by the USA government [1]. In 1992, the 'creation' of gene therapy approach by Anderson., *et al*. [2] was followed the same year 1992/93 by the 'creation' of cancer gene therapy or cancer immuno-gene therapy by Trojan., *et al* [3]. The cancer immuno-gene therapy was applied in clinical trial in parallel with cancer immunotherapy "created" in 1993/94 by groups of Townsend and Allison, and of Guo [4,5]. The cancer gene therapy was oriented at first for the treatment of one of the most malignant brain tumor - GM. The incidence of GM is between 3 - 8 cases per 100,000 people in Europe and North America [6].

The investigations on neoplastic development of the brain have demonstrated that IGF-I plays the principal role in glial differentiation, including especially GM [6]. IGF-I, as a mediator of Growth Hormone, Thyroid-stimulating hormone (TSH), glucose metabolism, is acting locally with autocrine/paracrine, with a predominant role in cancer development compared to other growth factors. Moreover, IGF-I has been reported to block the apoptosis [7]. The over-expression of IGF-I, accompanied by its high serum concentration, is an anticipatory signal of GM development [3].

Logically, to stop the GM development, the IGF-I was targeting on molecular levels using anti-gene technologies to stop the synthesis of IGF-I: on translation level - AS [8,9] and on transcription level - TH [10,11]. These techniques were applied *ex vivo* in cancer cells provided from surgical biopsies. Like that, the genetically modified cancer cells-transfected *in vitro* using IGF-I AS and TH vectors, and accompanied by apoptotic phenomenon, while injected in vivo have induced the immune anti-tumor response (Figure 1).

The cellular immunotherapy was done applying three subcutaneous injections (with interval of one month) of 0,5 millions of transfected AS/TH cancer cells irradiated with 5000 cGy gamma (Co60 or Cs137). The Peripheral Blood Lymphocytes, PBL cells, were examined in the blood samples removed before injection, and then three weeks after every injection. The PBL cells of treated patients, labelled for CD molecules (examined by flow cytometry analysis), have shown the significant increase of CD8 and CD28 molecules confirming the immune mechanism of used technologies (Figure 1). The median survival of the GM patients treated in USA and Europe, was as 21 - 24 months, and in some cases 3 and 4 years were signaled [6,12].

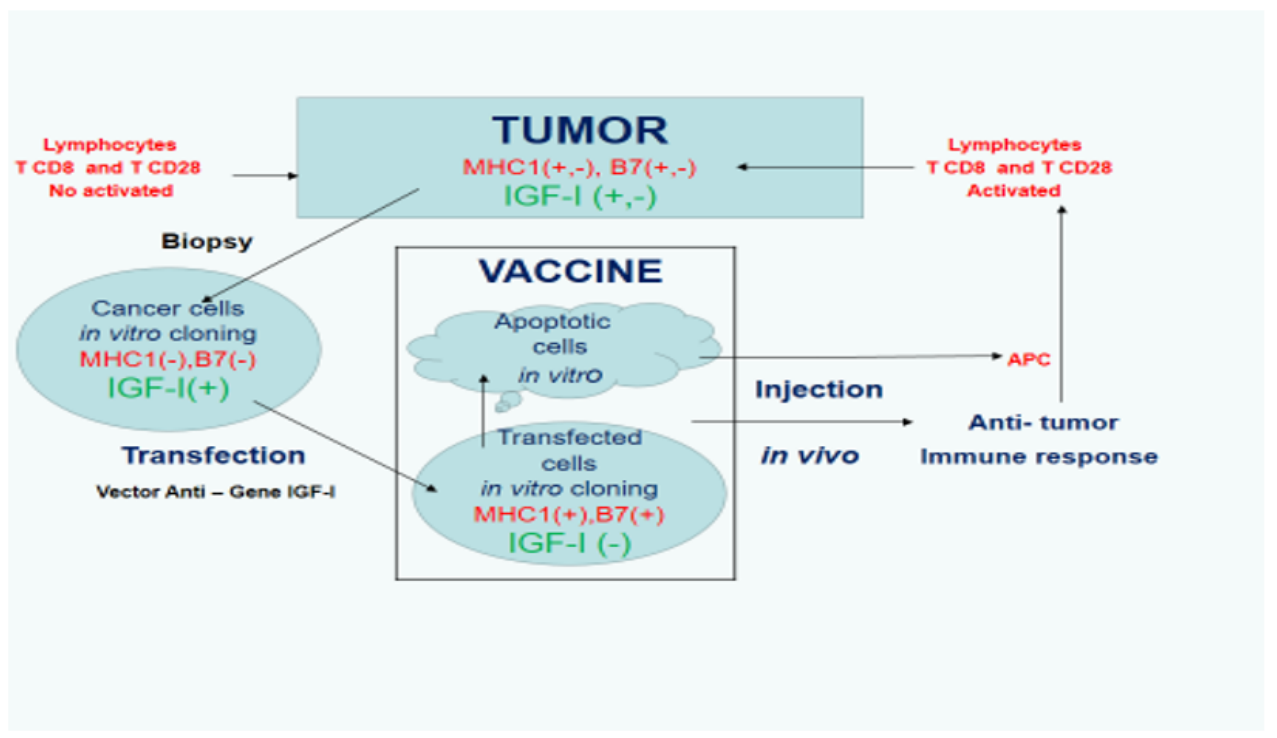

Figure 1: *Schema of cancer immunogene therapy. The cancer cells isolated from tumor biopsy are growing in tissue culture. The established cell line, after cloning, is transfected by the vector of anti-gene type (AS and TH IGF-I) [3,13]. The transfected cells, after cloning, and originated apoptotic cells, are injected in proportion 50 - 50 ('vaccine') in the cancer patients. The cellular presence of MHC-1 and B7 molecules, as well as induced immune response mediated by T lymphocytes CD8 and CD28, and Antigen Presenting Cells, APC cells, participate in immunogene mechanism [6].*

Conclusion

The treatment options for patients with advanced malignant brain tumor - GM (current mortality 100%), being limited in efficacy, therefore the search for new strategies constitutes a permanent challenge. Using chemotherapy the survival has reached 14 months and rarely 18 months. The immunotherapy, and especially imunogene therapy targeting growth factors, are currently among the most promising approaches for treatment of cancer diseases. Cancer immunogene therapy of anti-gene IGF-I approach, after being introduced in USA and Europe, was introduced recently in South America [Wikipedia-Gene therapy-1990s-2010s].

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