THE EPISTEMIC BASES OF THE ANTITUMOR BIOTHERAPIES: PRINCIPLES OF PNEI THERAPY OF CANCER.

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The psychoneuroendocrinoimmune (PNEI) pathogenesis of human cancer

The recent advances in the knowledgements of PNEI allowed a new interpretation of the neoplastic diseases as depending on an altered function of the PNEI system (1). Then, cancer progression does not depend only on genetic and histologic features of tumor mass, but also on the clinical status of the natural immunobiological resistance against cancer growth. A great number of clinical investigations have demonstrated the existence of several immune and endocrine anomalies in the advanced cancer patients (2).Therefore, cancer progression depends also on the presence of several endocrine, neuroendocrine and immune alterations, consisting of either an abnormal production, or a decreased secretion of the different hormones, neurohormones and cytokines.

The main cancer-related endocrine deficiency is consisting of the progressive decline in the nocturnal production of the pineal hormone melatonin (MLT) (3).

This finding is not a simple epiphenomenon, since the pineal gland represents the most important anticancer organ in the human body (4).This statement is justified by the fact that pinealectomy stimulates tumor growth, whereas the exogenous administration of MLT and other pineal hormones may inhibit cancer growth (4).However, in experimental conditions the administration of MLT may abrogate only partially, but not completely the stimulatory effect of pinealectomy on cancer development. Then, MLT would not be the only anticancer hormone released from the pineal gland. In fact, another pineal hormone, the 5-methoxytryptamine,has appeared to exert in vitro an anticancer activity superior to that of MLT itself (5). MLT is the most known pineal hormone, which is namely produced during the dark period of the day according to a circadian secretion,with high levels during the night and low values during the day . MLT has been proven to exert anticancer properties only when it is given at pharmacological doses and during the dark period of the day, according to its physiological light/dark circadian rhythm (6). MLT may synthetize per se the main anticancer mechanisms exerted by the commonly used conventional antitumor agents,

including 1) cytotoxic or cytostatic action on cancer cells 2) immunomodulatory activity, namely consisting of stimulation of IL-2- and IL-12-depended anticancer immune responses, corresponding to an antigen-independent and an antigen-depended antitumor cytotoxicity, respectively 3) cytodifferentiating effect on cancer cells by modulating oncogene expression 4)inhibition of EGF-receptor activation 5) anti-angiogenic activity. Another fundamental cancer-related endocrine alteration is consisting of an exaggerated cortisol secretion associated with a suppression of its circadian rhythm, which has been proven to play a negative prognostic significance. As far as the immune status is concerned, the main cancer-related immune alterations are represented by a decreased production of

IL-2 and IL-12,which are the main antitumor cytokines in humans, and by an enhanced secretion of immunosuppressive cytokines, such as IL-6,IL-10 and TGF-beta (7).Since the immune system is under a physiological PNEI modulation ,which mediates the influence of emotions and consciousness status on the immune functionless, cancer-related immunodeficiency would be at least in part the consequence of an altered PNEI regulation of the immune system, rather than to be due to a primary defect of immune cells.

The history of the biotherapies of cancer

The historical limits of the treatment of cancer with natural agents may be summarized, as follows: the mention of single cases who had obtained some benefits, rather than adequate clinical case-series 2) empiristic results rather than the exact definition of the specific mechanisms of action 3)direct translation from the in vitro data to the treatment of patients without preliminary clinical trials. On the contrary, according to the recent advances in the area of PNEI, the end-points of the complementary therapies of cancer would have to consist of: 1) therapeutic proposal after the failure of the conventional antitumor therapies, including surgery, chemotherapy, radiotherapy, endocrine therapy, anti-growth factor and anti-angiogenic therapies and immunotherapy 2)association with the standard anticancer therapies to enhance their efficacy or to reduce their toxicity 3)palliative therapy of cancer-related symptoms. At present, it is known the existence of several natural antitumor agents, but it is fundamental to put into evidence the different therapeutic importance of the single natural agents, according to the following classification based on their different therapeutic potency: 1) endogenous factors produced by human body itself (pineal hormones, somatostatin, oxitocin, DHES ,endogenous cannabinoids) 3) phytotherapeutic agents

provided by a scientifically documented anticancer activity (curcumin, Echinacea, arabinoxylan, antitumor mushrooms) 4)various natural substances with not well established antitumor properties.

The PNEI therapy of cancer

The rationale of the PNEI therapy of cancer simply consists of the restablishment of the PNEI status of health through the exogenous administration of those hormones and cytokines, whose production is progressively diminished with cancer progression. In more detail, according to a PNEI approach, the aim of the biotherapies of cancer is founded on 3 major objectives:

1) to correct cancer-related pineal deficiency through the administration of MLT during the night and 5-methoxytryptamine during the day
2) to correct the major immune deficiencies by the direct exogenous administration of IL-2 and IL-12,or by that of natural agents capable of stimulating IL-2 and/or IL-12 production (Aloe, Myrrh, anticancer immunomodulating mushrooms)
3) 3) to exert an antitumor antiproliferative action by the administration of natural agents provided by cytotoxic, cytostatic, cytodifferentiating or anti-angiogenic properties on tumor cells (Aloe, Myrrh, curcumine, cannabinoids, retinoids, vitamin D)

The history of the clinical trials with MLT, which is the most investigated natural anticancer agent, may be synthetized, as follows:

1) MLT alone as a palliative therapy of cancer, in particular for the treatment of the neoplastic cachexia, thrombocytopenia, neurotoxicity, cardiotoxicity and asthenia

2) Neuroimmunotherapy with MLT plus subcutaneous low-dose of IL-2(to enhance the antitumor activity of IL-2)

3) Chemoneuroendocrinotherapy with MLT plus the commonly used chemotherapeutic agents (on the basis of the fact MLT is one of the most active natural anti-oxidant agents, which have appeared to enhance the cytotoxic potency of the chemotherapeutic drugs)

4) Neuroendocrine therapy with standard endocrine therapy plus MLT (to enhance the hormone-dependency of tumors)

5) Radioneuroendocrine therapy with radiotherapy plus MLT(to enhance the radiosensitivity of tumors)

6) Biotherapy with MLT plus other natural anticancer biological agents (Aloe, Myrrh, curcumine, anticancer mushrooms).

In the untreatable metastatic solid tumor patients, who failed to respond to the conventional anticancer therapies and with a life expectancy less than 1 year, MLT alone has allowed a 1-year percent of survival of about 30%.The 1-year percentage of survival may be further enhanced by the concomitant injection of low-dose IL-2,with a percent of 50% and 9% at 1 and at 3 years, respectively (7).

References

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