REVIEW ARTICLE

The psychoneuroendocrine-immunotherapy of cancer: Historical evolution and clinical results

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The prognosis of the neoplastic diseases depends not only on the biogenetic characteristics of cancer cells but also on the immunological response of patients, which may influence the biological features of cancer cells themselves as well as the angiogenic processes. Moreover, the immune system *in vivo* is under a physiological psychoneuroendocrine (PNE) regulation, mainly mediated by the brain opioid system and the pineal gland. In more detail, the anticancer immunity is stimulated by the pineal hormone melatonin (MLT) and inhibited by the opioid system, namely, through a mu-opioid receptor. Several alterations involving the pineal endocrine function and the opioid system have been described in cancer patients, which could play a role in tumor progression itself. Therefore, the pharmacological correction of cancer progression-related anomalies could contribute to control cancer diffusion, namely, the pineal endocrine deficiency and the hyperactivity of brain opioid system. In fact, the administration of pharmacological doses of the only MLT has already been proven to prolong the 1-year survival in untreatable metastatic cancer patients. Better results may be achieved by associating other pineal indoles to MLT, mu-opioid antagonists, cannabinoids, beta-carbolines. Moreover, these neuroendocrine combinations may be successfully associated with antitumor cytokines, such as interleukin (IL)-2 and IL-12, as a PNE-immune cancer therapy as well as with antitumor plants as PNE-phytotherapy of cancer in an attempt to propose possible anticancer treatments also to patients with disseminated cancer and untreatable according to the standard oncology.

Key words: Cancer disease, psychoneuroimmunology, pineal glande

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INTRODUCTION

The all medical oncological strategies available up to now in the treatment of human neoplasms have been elaborated in an attempt to counteract cancer dissemination through an inhibition of cancer cell proliferation by inducing the apoptosis of by blocking the angiogenetic processes, which are essential for tumor biological malignancy. However, it has to be remarked that tumor growth does not depend only on the genetic characteristics of cancer cells but also on the immune status of cancer patients.[1-3] Then, the limit of the conventional anticancer therapies available up to now, including the more recent target therapies, is consisting of the exclusion of the importance of the immune status of cancer patients in determining their prognosis. In fact, a great number of immune alterations have been described in cancer patients, which would play a role in influencing the clinical history of the neoplastic disease.[1-4] Moreover, because of the existence of a neuroendocrine regulation of the immune system, as shown by the recent advances in the knowledge of the psychoneuroendocrine-immunology (PNEI),[5,6] cancer-associated immune alterations occurring at the beginning of the disease could be due at least in part to an altered psychoneuroendocrine (PNE) control of the antitumor immune response. Then, at least from a theoretical point of view, it could be possible to correct cancer-related immune alterations by acting on the PNE regulation of the immune system.

The PNE therapy of cancer consists of the replacement of the psychoneuroimmune conditions of the status of health by a pharmacological correction of the major

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cancer progression-related alterations involving the neuroendocrine regulation of the anticancer immunity. This project is justified by the fact that cancer-related immunosuppressive status would depend, at least at the beginning of cancer development, on an altered neuroendocrine regulation of the immune system since it is only with cancer dissemination that tumor mass itself may produce immunosuppressive substances, such as interleukin IL-10 and transforming growth factor (TGF)-beta,[7] which further suppress the already altered function of the immune system. Then, a pharmacological correction of cancer-related neuroendocrine alterations involved in the control of the antitumor immunity could improve the immune functionless of cancer patients. Several neuroendocrine alterations have been described in advanced cancer patients, such as the disappearance of cortisol circadian rhythm in many tumor histotypes[8] and abnormally high levels of prolactin, namely, in breast and prostate carcinomas,[9] but the main cancer progression-related neuroendocrine deficiency consists of a progressive decline in the nocturnal production of melatonin (MLT),[10] which represents the most investigated, but not the only, indole hormone provided by anticancer activity produced by the pineal gland. The mechanisms of the antitumor action of MLT have been well investigated, and at present, MLT would represent the only molecule existing in the nature, which is potentially able to inhibit the overall phases of cancer development and progression,[11-15] consisting of (1) the existence of a previous immunosuppressive status due to an altered neuroendocrine control of the immune system related to stress and depression; (2) spontaneous or carcinogen-induced malignant transformation of a single cell; (3) the alteration of intracellular junctions; (4) the change in the intercellular matrix following an alteration of intercellular junctions, which stimulates the angiogenesis; (5) angiogenesis-induced cancer invasion and dissemination, with tumor production of immunosuppressive substances; (6) tumor expression of FAS-ligand, which may induce apoptosis of FAS-expressing T-lymphocytes.

Methods

In this review article, we used keywords such as "MLT," "neuroimmunomodulation," or "pineal gland" in PubMed to evaluate possible anticancer treatments for patients with disseminated cancer and untreatable according to the standard oncology.

THE PHYSIOPATHOLOGY OF THE ANTICANCER IMMUNITY

It is known that immune system-induced destruction of cancer cells is mainly mediated by T cytotoxic lymphocytes (CD8+) and NK cells (CD16+), respectively, through an antigen-specific and an antigen nonspecific cytotoxicity.[16] NK cells are mainly stimulated by IL^{-2} released by T helper-1 (TH1) lymphocytes (CD4+) while T cytotoxic lymphocytes (CD8+) are namely under a stimulatory control released by IL-12 produced by the dendritic cells.[17] On the other hand, the anticancer immunity is inhibited by the activation of the macrophage system through the production of suppressive cytokines, such as IL-6 and T regulatory (T reg) lymphocytes (CD4+CD25+), which counteract the anticancer immunity by producing immunosuppressive cytokines inhibiting the secretion of both IL-2 and IL-12, including TGF-beta and IL-10, or by a direct cell-cell contact.[18-20] Therefore, the knowledge of the mechanisms responsible for the anticancer immunity is essential to identify which immunobiological alterations may have a prognostic significance in influencing the clinical history of the neoplastic disease.

THE PSYCHONEUROENDOCRINE CONTROL OF CANCER GROWTH AND ANTITUMOR IMMUNITY

During the long history of the human war against cancer, several experimental strategies have been elaborated to promote both spontaneous and carcinogen-induced cancer onset and to stimulate cancer dissemination in tumor-bearing animals, the most important of them would be represented by stress conditions[21] and by pinealectomy.[22] Each hormone, neurohormone and neurotransmitter may potentially influence the immune system, but the recent discoveries of PNEI[23-25] have allowed to identify three main anatomic structures responsible for the physiological PNE regulation of the immune responses, consisting of brain opioid system, brain cannabinergic system, and the pineal gland. Pineal gland and cannabinergic system would constitute a functional axis,[23] which plays an important role in the stimulation of the anticancer immunity, namely, by directly promoting IL-2 production by TH-1 lymphocytes.[24] In contrast, brain opioid system may inhibit the anticancer immune response by stimulating the immunosuppressive function of T reg lymphocytes.[25] Stress condition - promotion of cancer growth would be due to a chronic-enhanced production of cortisol, whose immunosuppressive effects are well known, and to an enhanced brain opioid system activity,[21] which may be abrogated by the administration of mu-opioid antagonists. At the other side, it is known since more than 50 years that the surgical removal of the pineal gland or its pharmacological inhibition may enhance the frequency of both spontaneous or carcinogen-induced tumors.[22,26] The promoting effect of pinealectomy on tumor growth may be only partially abrogated by the administration of MLT,[27] by suggesting that pineal hormones other than MLT are involved in the anticancer activity of the pineal gland.[28] The importance of the neuroendocrine status of

patients in cancer progression is confirmed by the fact that in experimental conditions, the pharmacological neutralization of cancer development-associated changes in neurotransmission may oppose tumor onset.[29] Therefore, cancer-related neuroendocrine alterations would not represent a simple epiphenomenon, but they could play a physiopathological role in cancer progression.

PINEAL ENDOCRINE DEFICIENCY AND CANCER PROGRESSION

The most frequent neuroendocrine alteration occurring with cancer progression is represented by the progressive decline in the nocturnal production of MLT,[30] with a following disappearance of its physiological light/dark circadian rhythm. Because of its antitumor activity,[11-15] cancer progression-related MLT deficiency could contribute at least in part to tumor dissemination itself. The progressive decline in MLT blood levels would depend on tumor production of the enzyme indoleamine-2,3-dioxygenase,[31] which may induce a depletion of tryptophan, that is, essential for both MLT synthesis and the anticancer immunity since tryptophan deficiency inhibits TH1-lymphocyte functions and stimulates T reg lymphocyte activation, with a following suppression of the anticancer immune response. In addition, histological alterations of the pineal gland had been already described in patients died from cancer since more than 50 years ago.[32] Therefore, MLT deficiency would not constitute the only pineal endocrine defect occurring during the clinical history of the neoplastic disease. In fact, the pineal gland has been proven to produce several anticancer natural molecules other than MLT; in particular, the indole hormone 5-methoxytryptamine, which *in vitro* has appeared to exert an anticancer antiproliferative activity superior to that of MLT itself,[33] and a great variety of beta-carbolines, which may play both antitumor and psychotropic effects in terms of expansion of mind, the most active of them is the 6-methoxy-1,2,3,4 tetrahydro-beta-carboline, also called pinoline or pinealine.[34] At present, however, the only well-investigated anticancer properties are those of MLT.[11-15]

THE CLINICAL HISTORY OF THE PSYCHONEUROENDOCRINE THERAPY OF CANCER

On the basis of the fact that cancer growth is inhibited by the pineal gland and is stimulated by brain opioid system, namely, through the activation of mu-opioid receptors,[21-27] the PNE therapy of cancer is consisting of the administration of endogenous human neuroendocrine molecules provided by anticancer activity, due to a direct antiproliferative action and/or a stimulation of the anticancer immunity, in association with pharmacological strategies performed to counteract its suppression, such as the use of the mu-opioid antagonist naltrexone (NTX).

From a historical point of view, the evolution of PNE approach in cancer therapy may be summarized into 5 main consecutive clinical phases, consisting of (1) the oral administration of pharmacological doses of the only MLT during the dark period of the day[35] as shown by Bartsch and Bartsch[36] corresponding to the daily period of its maximal endogenous production; (2) the administration of other pineal antitumor indole hormones in association with MLT, namely, the 5-methoxy-tryptamine (5-MTT) during the light phase of the day in an attempt to pharmacologically reproduce the physiological light/dark rhythm of the pineal gland;[37] (3) the administration of the mu-opioid antagonist NTX to block the opioid system, which plays a stimulatory role on cancer growth and an inhibitory one on the anticancer immunity;[38] (4) the administration of cannabinoid agonists to counteract cancer-related hyperactivity of the macrophage system,[39] which may suppress the anticancer immunity and stimulate cancer growth by producing tumor growth factors and angiogenic molecules; (5) the administration of beta-carbolines, such as the pinoline.

All clinical data are referred to untreatable metastatic cancer patients, for whom no other antitumor standard treatment was available, and with life expectancy <1 year.[40] Moreover, most studies have been performed with MLT alone and at a mild pharmacological dose consisting of 20 mg/day in the dark phase of the day.[35,40] MLT at a daily dose of 20 mg has appeared to induce a survival time longer than 1 year in about 30% of advanced cancer patients with life expectancy <1 year,[35] in association with an improvement in their clinical status, in particular in the treatment of cachexia, depression, and thrombocytopenia. The antidepressant and the thrombopoietic properties of MLT have appeared to be enhanced by a concomitant administration of the other pineal indole 5-MTT.[37] Moreover, it has been recently demonstrated that the anticancer activity of MLT in humans is a dose-dependent phenomenon since MLT at 100 mg/day has appeared to induce a disease stabilization in cancer patients, who had progressed under a dose of 20 mg, and to determine a survival time >1 year in about 50% of patients with life expectancy <1 year,[41] in association with a percent of objective tumor regressions of about 10%, whereas they are extremely rare at a dose of 20 mg/day. On the contrary, the therapeutic role of the mu-opioid antagonists in cancer therapy is still controversial, since two different schedules have been proposed, consisting of low-dose and high-dose NTX.[42,43] Preliminary clinical results would suggest the concomitant administration of high-dose NTX may enhance the anticancer activity of MLT, at least in the treatment of brain tumors.[44] As far as, the clinical use of cannabinoids in cancer therapy is concerned, it is still at the beginning. However, preliminary data would suggest that cannabinoids may be effective in the palliative therapy of

tumors to cure cachexia, anorexia, vomiting, and also pain in association with opioids.[45] Moreover, preliminary data would seem to show that cannabinoid agonists may increase the efficacy of MLT in the therapy of brain glioblastoma.[44] Finally, the administration of beta-carbolines, such as the pinoline, in association with MLT and the other pineal indoles would further improve the consciousness status of the untreatable metastatic cancer patients and their mode (unpublished data).

THE FUTURE EVOLUTIONS OF THE PSYCHONEUROENDOCRINE THERAPY OF CANCER

The anticancer efficacy of a PNE approach to cancer therapy may be further enhanced by at least two main strategies, consisting of its association with anticancer cytokines, namely, with IL-2 and IL-12, as a PNEI therapy of cancer, or with the administration of anticancer natural plants, namely, *Aloe vera* and *Arborescens, Myrrh, Magnolia, Boswellia, Curcuma*, and *Annona muricata* as a PNE-phytotherapy of tumors. The main anticancer molecules are represented by aloe-emodin for *Aloe*, *Guggulsterone* for *Myrrh*, and *Honokiol* for *Magnolia*.[45-47] MLT has appeared to enhance the antitumor efficacy of low-dose IL-2 in terms of both tumor response and survival time with respect to IL-2 alone,[48] with potential activity in most tumor histotypes, whereas IL-2 is generally effective only in the treatment of renal cancer and melanoma. Moreover, at present, the maximum lymphocytosis achieved on treatment has been obtained with IL-2 plus IL-12 under a neuroendocrine modulation with MLT.[49] On the same way, the antitumor efficacy of MLT in untreatable cancer patients with life expectancy <1 year may be increased by the concomitant administration of *Aloe*, *Myrrh*, *Magnolia*, and *Boswellia*, with a greater percentage of tumor regressions and a 1-year survival of about 50% of patients.[50]

Finally because of its fundamental immunoregulatory role,[5,6] MLT could be successfully associated with the recent immunotherapies with checkpoint inhibitors[51] to pilot the immune response in an antitumor way by stimulating lymphocyte proliferation and counteract that of monocytes which in contrast may suppress the antitumor immunity, with a consequent increase in lymphocyte-to-monocyte ratio that represents one of the most simple clinical parameters, able to predict the efficacy of the various anticancer therapies.[52]

Therefore, in conclusion, it is possible to affirm that the PNEI approach in cancer therapy may offer new therapeutic strategies in patients with disseminated cancer, for whom no other standard anticancer therapy is available.

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Conflicts of interest
The authors have no conflicts of interest.

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