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The Personalization of Cancer Cure: Reality or Illusion?

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Abstract

It is known that the prognosis of the neoplastic diseases does not depend only on tumor characteristics, including lesion extension, histology and genetic profile, but also on the biological response of patients, which depends on both immune and endocrine variables, since the immune system is physiologically under a psychoneuroendocrine regulation. Therefore, a synthetic clinical evaluation of the endocrine and immune functions either prior to the various anticancer therapies or under treatment is essential for realizing an adequate investigation of the mechanisms involved in the clinical course of the neoplastic disease. In more detail, the prognosis of several tumors, irrespectively of their histology and extension, has appeared to be worse in the presence of alterations of cortisol rhythm, a reduced pineal secretion of melatonin during the night, lymphocytopenia, low T-H1 cell count, high T regulatory lymphocyte number, and abnormally high PRL levels for the only metastatic breast and prostate tumors. The pharmacological correction of the main endocrine, neuroendocrine and immune alterations occurring during the clinical course of the neoplastic disease could improve the prognosis and the efficacy of the various anticancer therapies. Moreover, the immune system in vivo is under a physiological psychoneuroendocrine 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 hyper-activity 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, β-carbolines. Moreover, these neuroendocrine combinations may be successfully associated with antitumor cytokines, such as IL-2 and IL-12 as a psychoneuroendocrinoimmune cancer therapy, as well as with antitumor plants as psychoneuroendocrinophytotherapy of cancer, in an attempt to propose possible anticancer treatments also to patients with disseminated cancer and untreatable according to the standard Oncology. The main novelty is to refer the personalization of cancer cure not only in relation to the biogenetic characteristics of the tumor of the single patients, but also to the biological characteristics of each cancer patient, namely the immune status in terms of antitumor immunity.

Keywords: Melatonin (MLT); IL-2; IL-12; TH1; T reg; Psichoneuroimmunotherapy

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Introduction

The concept of a personalization in the treatment of human tumors is extremely ambiguous from the point of view of the clinical management of a disease, which remains still untreatable in its disseminated metastatic phase, despite the great advances in its technological approaches. In fact, the idea of cancer care personalization is generally interpreted in only two significances, which are both ambiguous, since they do not really reflect the biological status of cancer patients, being consisting of the former in a simple generic human behaviour in the relation between clinicians and patients, and the latter in the identification of the best therapy on the basis of the only tumor biological characteristics, including histology, grade, hormone or growth factor receptor expression, and cancer cell genetic mutations. The human behaviour of clinical Oncologists is fundamental in an attempt to establish together with the patients the therapeutic program, its rationale and aim, and the type of chemotherapy or other conventional endocrine or immunological treatments, and the duration of cancer treatments, but it is not sufficient if it is limited to a generic emotional relationship. On the same way, the personalization of cancer therapy on the basis of the only tumor bio-genetic features cannot be considered as a real personalised clinical management of cancer patients, since this kind of personalization would exclude not only the psycho spiritual status of patients, but also their endocrine and immune status, which would determine the efficacy or the failure of the natural immune biological resistance against cancer development and progression. Then, a real and true personalization of cancer therapy, which may be founded on the basis of scientific evidences and not only on emotional aspects, would have to take into consideration the functional status of the antitumor immunity in each single oncology patient, which has been proven to depend not only on the activity of the immune system, but also on its physiological psychoneuroendocrine regulation [1], that reflects the psychological and spiritual life of patients themselves in addition to other variables, such as dietary regimen and the style of life. The importance of the evaluation of the immune status of patients is generally taken into consideration by the Oncologists only during the immunotherapeutic approaches in cancer therapy, whereas in contrast it would have to be considered in every possible kind of cancer cure, since the efficacy of chemotherapy itself has appeared to depend also at least in part on the immune response of patients. In fact, recent clinical investigations have shown that the immunosuppressive activity of cancer chemotherapy is limited to the only anti-microbial immunity, including the anti-bacterial and the anti-viral immune reactions, whereas it could also improve the functionless of the antitimor immunity through a modulation of the cytokine network [2], which is influenced by the different chemotherapeutic agents [3], even though only few data are available about the relationships between chemotherapy and endogenous secretion of cytokines, which influence the grade of efficacy of the antitumor immune response. On the contrary, the condition of cancer patients is generally taken into consideration only in terms of performance status [PS], which has been proven to constitute one of the main prognostic factors in human neoplasms [4]. However, it has to be remarked that PS may influence the clinical history of the neoplastic and the prognosis of cancer because of its effects on the immune functionless, and in particular it has been proven that a poor PS is associated with a suppression of the anticancer immunity [5]. Obviously, the personalization of cancer cure on the basis of the endocrine and immune status of cancer patients is not alternative to the standard, then it does not exclude the importance of the analysis of tumor histological and genetic features, but on the contrary it is a complementary approach, since the biological characteristics of tumor are the results of a complex interactions between cancer cell differentiation and proliferation, and the efficacy of the immune antitumor reactivity, by considering the bio-immune-psycho spiritual status of patients as the main and the most synthetic prognostic factor in the neoplastic diseases. Then, the bio-immune-psycho endocrine status of cancer patients would have to be considered as the main and the most synthetic prognostic factor in the neoplastic diseases, and patients themselves are the main prognostic variable for their cancer [6,7].

Tumor-dependent prognostic variables

It is commonly accepted that the main tumor variables influencing the therapeutic decisions for all kinds of cancers are represented by the histology, the grade of malignancy and the extension of disease. In contrast, other variables are different and specific in relation to the single histotype of tumor, and they regard tumor expression of receptors for hormones or for tumor growth factors, such as epidermal growth factor (EGF), and the functional status of cell proliferation related genes [8,9]. The determination of these variables is fundamental to establish the optimal therapy and the type of clinical management of the neoplastic disease, but they are generally limited to the investigation of the only tumor biology, which is apparently independent from the biological response of cancer patients. Tumor variables may influence both the prognosis and the best therapeutic decision. At present, the main tumor variables clinically taken into consideration are represented by Estrogen Receptor (ER) expression for breast cancer, androgen receptor expression for prostate carcinoma, HER-2 over expression for breast cancer, and at least in part for gastric cancer, the lack of mutation, the so-called wild type status, of EGF-receptor (EGF-R), K-Ras and N Ras for colorectal cancer, ALK positivity and EGF-R mutations for lung adenocarcinoma, and BRAF mutation for melanoma [10-14]. ER expression predicts the efficacy of anti-estrogen and aromatase inhibitor therapy in breast cancer, while that of HER-2 would predict the clinical activity of anti-HER-2 Monoclonal Antibodies [MABs] in breast cancer and all test in part in gastric cancer. The lack of EGF-R, K-Ras and N-Ras mutations is associated with a greater efficacy of anti-EGF-R MABs in colorectal cancer. In contrast, the evidence of EGF-R or BRAF mutations would predict the efficacy of anti-EGF-R drugs in lung adenocarcinoma and that of anti-BRAF agents in malignant melanoma. On the other hand, the response to cancer immunotherapies with MABs against checkpoint immune molecules, namely CTLA-4 and PD-1 or its ligands 1 and 2, may be predicted on the basis of CTLA-4 and PD-1 expression, respectively, in tumor microenvironment. [10-12]. However, despite it was

hypothesized the necessity of PD-1 or CTLA-4 expression to achieve a clinical response to immunotherapies with anti-PD-1 and anti-CTLA-4 MABs, respectively, successive studies have shown that a disease control may be obtained also in patients with low or absent expression of these molecules, by suggesting the possible involvement of other immune mechanisms capable of influencing the immuno-biological reactivity of cancer patients [13], in particular the profile of tumor T lymphocyte infiltration, with different prognostic profiles depending of the type of T lymphocyte subsets, with a more favourable prognosis in the presence of T H1 [$CD4^+$] lymphocyte infiltration and with a worse prognosis when the most frequent tumor infiltrating T cells are represented by PD-1 or CTLA-4 expressing T regulatory [T reg] lymphocytes [$CD4^+CD25^+$], which may suppress the antitumor immunity by blocking the endogenous production of both IL-2 and IL-12, which are the main antitumor cytokines in humans [14]. On the contrary, no biological parameter would see to predict the efficacy of anti-angiogenic anti-vascular endothelial growth factor [VEGF] agents, including anti-VEGF MABs and small anti angiogenic molecules.

Prognostic variables related to immune and endocrine response of cancer patients

A real personalization of cancer therapy which may be considered as really founded on scientific physio-pathological bases and not only on simple emotional behaviours and on generic psychological aspects, would have primarily to take into consideration the endocrine, psychoneuroendocrine and immune status of cancer patients existing prior to the start of therapy, as well as their immuno-endocrine biological response during the various antitumor therapies. This statement is justified by the evidence that cancer progression is associated with the appearance of several endocrine and immune alterations, some of them have been proven to deserve a prognostic significance [15]. Then, an eventual pharmacological correction of these anomalies could improve the clinical control of tumor growth itself, by confirming that the neoplastic disease is a systemic pathology just already at the beginning of its development. From a clinical point of view, we have to consider both endocrine and immune cancer progression-related alterations:

I) **Prognostic cancer-related endocrine alterations:** The main tumor progression associated endocrine and neuroendocrine anomalies potentially provided by a negative prognostic significance in terms of both survival time and response to therapy, may be summarized, as follows:

Lack of cortisol rhythm or presence of hyper-cortisolemia: The evidence of an altered cortisol rhythm, which is a sign of a desynchronization condition probably due to the stimulatory action of pro-inflammatory cytokines on the hypothalamic pituitary-adrenal axis and which may occur in several tumor histotypes, including lung, breast and ovarian carcinomas, has appeared to predict a poor prognosis [16,17]. Moreover, the efficacy of chemotherapy has been shown to be associated with a normalization of cortisol rhythm in lung cancer patients [18].

Progressive decline in the nocturnal production of melatonin [mlt]: The most investigated anticancer hormone produced by the pineal gland [19], with a following disappearance of its physiological light/dark circadian rhythm [20]. MLT deficiency would constitute the main cancer-related endocrine deficiency, which could be involved at least in part in promoting tumor progression, because of its anticancer activity, since the pineal gland plays a fundamental role in the natural resistance against cancer development and dissemination by exerting both antiproliferative and immunomodulating actions [21]. In addition, because of its functional role as a central regulator of the cytokine network and immune endocrine interactions [22,23], pineal endocrine deficiency could contribute to explain the great number of cancer-related neuroendocrine and immune alterations, involving both cytokine secretions and immune cell subsets.

Hyper-prolactinemia: The evidence of abnormally high PRL levels has appeared to be associated with poor prognosis and reduced efficacy of the antitumor therapies in metastatic breast and prostate carcinomas [24,25], being PRL a growth factor for mammary and prostate tumors [26,27]. Similar negative prognostic considerations could probably regard the evidence of enhanced blood levels of alpha-MSH in patients with malignant melanoma, being alpha-MSH a growth factor for melanoma cells, which in contrast are inhibited by the pineal hormone MLT [23]. The importance of better investigating cancer-related endocrine systemic alterations provided by a negative prognostic significance is further justified by the possibility of their corrections through a simple hormonal manipulation with long acting dopaminergic agents, such as bromocriptine and cabergoline, for the treatment of hyper-prolactinemia [28], with aminoglutethimide for blocking the enhanced cortisol production, and finally with MLT endocrine replacement therapy to correct the pineal endocrine deficiency [29,30].

ii) **Prognostic cancer-related immune alterations:** Within the great number of cancer-related immune anomalies, some alterations have been proven to deserve a prognostic significance by conditioning tumor progression, particularly as follows:

Lymphocytopenia: It is known since more than 40 years that lymphocytopenia represents one of the most important and universally generalized negative prognostic factors in cancer patients for most solid tumor histotypes [6]. Then, lymphocytopenia, either before the various antitumor therapies, or in response to therapies themselves, would represent the main and the simplest negative immune prognostic factor related to the biological response of cancer patients. Not only, but in addition the evidence of lymphocytopenia prior to the different anticancer treatments, including immunotherapy with cytokines such as IL-2 [31] or with anti-immune checkpoint MABs [32] and chemotherapy itself [33], has been proven to predict a lack of response to the different anticancer therapies. The prognosis is particularly poor when tumor cells may express FAS-L [34], since their contact with FAS-expressing T lymphocytes may induce the apoptotic death of T lymphocytes themselves instead of that of cancer cells.

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Decreased number of T helper-1 [TH1] [CD4$^+$] lymphocytes: The progressive decline in T-H1 cell count [35], with a consequent concomitant decline in the endogenous production of IL-2, which represents the main growth factor for T lymphocytes [36], would constitute the most prognostically negative immune alteration involving T lymphocyte subsets occurring during the history of cancer.

Increase in T reg cell number: The evidence of a progressive enhancement of T reg cell count has appeared to be associated with poor prognosis, by reflecting the existence of an immunosuppressive status of the anticancer immunity [37].

Increase in the absolute number of lymphocytes: Irrespectively of the type of anticancer therapy, including immunotherapy with IL-2 [38] and chemotherapy itself [39], the evidence of an acute lymphocytosis or at least of a progressive increase in lymphocyte count in response to the various anticancer treatments, would represent at moment the most simple clinically important favourable prognostic factor in terms of both survival and response to therapy. Then, in the presence of a similar radiological response in terms of tumor regression or disease stabilization, lymphocyte behaviour could predict the different durations of the response, which would be probably longer in patients, whose radiological objective tumor regression is associated with a lymphocyte increase or at least with a lack of lymphocyte decrease [31-33]. Similar considerations may be suggested for VEGF behaviour, since a radiological evidence of disease control associated with a normalization of previously abnormally high VEGF levels has appeared to predict a longer duration of response with respect to that obtains in patients with similar radiological response, but with persistently high VEGF blood concentrations [40].

High blood levels of VEGF: The evidence of high pre-treatment levels of VEGF tends to negatively affect the efficacy of chemotherapy [40], which may exert biological events other than the cytotoxic activity, including anti-angiogenic and immunomodulating effects.

With the progressive development of new immunotherapeutic strategies in cancer therapy, namely those with MABs against immune checkpoints, the evaluation of the immunobiological response of patients turns to became clinically important, but it is generally limited to the only evaluation of the type of immune cells infiltrating the tumor mass [32]. On the contrary, an adequate evaluation of patient immune response would have to consider both tumor immune cell infiltration and changes in the number of lymphocytes and their subsets. Unfortunately, few data only are available about the relation between tumor cells and lymphocyte at the histological levels and the profile of lymphocytes in the circulating blood.

Conclusions and future perspectives

By considering not only the biological characteristics of the neoplastic lesions, including histology, grade of malignancy, genetic pattern and dimensions, but also the neuroendocrine and immune response of cancer patients, it has appeared that, irrespectively of the type of cancer treatments, each kind of antitumor strategy has to induce and to be associated with an increase in the absolute number of circulating lymphocytes, namely of T-H1 cells, to be really effective across the time and not only for a brief period of time. By synthetizing, a clinically real personalization of cancer therapy would require the determination of the blood levels of some endocrine and immune parameters reflecting the endocrine and immune conditions of patients, either prior to therapy, or under treatment, in an attempt to decide the optimal strategy of cancer cure for the single oncologic patient. Then, a real personalization of cancer cure cannot be simply limited to the only radiological and histological examinations, but it has to consider also the investigation of the endocrine and immune status of patients, and their variation on treatment. From a clinical point of view, to realize a true personalization of cancer therapy, either at the moment of the therapeutic decision or to monitor the efficacy of treatments, the following laboratory analyses would have at least to be routinarily included in the clinical management of the neoplastic disease:

1] Evaluation of cortisol circadian rhythm: By collecting blood samples at 8.00 A.M. and at 4.00 P.M. The lack of cortisol rhythm would be the expression of a desynchronization status with respect to the normal awake-sleep circadian rhythm, and it predicts a poor prognosis.

2] **Investigation of the pineal endocrine function:** A functional analysis of the pineal gland, which represent the most important anti-cancer organ in the human body [23], has to consist of at least the determination of MLT blood levels and its light/dark circadian rhythm by collecting blood samples in relation to the main phases of the photoperiod, or in an easier way by determining the daily and night urinary excretion of its main metabolite, the 6-Sulphatoxymelatonin [6-MTS] [41]. The progressive cancer-related MLT deficiency, namely during the night with a following disappearance of its light/dark rhythm, is the expression of a damage involving the neurochemical processes of the Neuro-immunomodulation, and it is associated with a poor prognosis [23]. On the contrary, a pharmacological correction of MLT deficiency through an exogenous administration would improve the efficacy of anticancer therapies, including chemotherapy itself [29,42].

3] Measurement of PRL blood levels in metastatic breast and prostate carcinomas: The occurrence of high PRL serum levels has appeared to be associated with lack of efficacy of the various anticancer treatments, including chemotherapy and endocrine therapy, and it may be corrected by the administration of dopaminergic agents [25-27]. In contrast, breast surgery- induced PRL increase has been proven to predict a better prognosis in terms of both lower frequency of recurrence and survival time [43], despite the potential tumor growth factor activity of PRL [44], and this evidence could be explained by considering that in formal conditions each breast manipulation, such as breast surgery, has to stimulate PRL secretion. Then, the lack of PRL increase in response to the breast surgery would reflect the existence of an evident alteration in the neuroendocrine control of PRL release.

4] **Synthetic evaluation of the antitumor immunity:** The functional

status of the antitumor immunity on each single patient may be established on the basis of the simple determination of at least the absolute number of circulating lymphocytes and T-H1/T reg lymphocyte ratio [39], which represents the end result of a great number of cytokine interactions, namely those of IL-2, IL-12, TGF-β, TNF alpha, IL-l0 and IL-6. The evidence of a progressive decline in T-H1 cell number associated with a concomitant and progressive increase in T reg cell count, with a following decrease in the value of T-H1/T reg ratio has been proven to predict a poor prognosis in metastatic cancer [39], being the expression of an immunosuppressive status, as the end results of a decrease in IL-2 and IL-12 levels and an increase in those of TGF-β, IL-6 and IL-l0. Then, the measurement of the different cytokines involved in modulating the anticancer immunity may be synthetized by the only determination of T-H1/T reg ratio. The clinical investigation of the immune condition of the single oncologic patient may allow improving the efficacy of cancer immunotherapies themselves. Then, in the presence of lymphocytopenia, which has appeared to reduce the efficacy of every anticancer treatment [39], including chemotherapy and immunotherapy with MABs, a short time therapy with Sub-Cutaneous [SC] low-dose IL-2, which is the main growth factor for T lymphocytes [36], could enhance the efficacy of anticancer therapies. In fact, a brief period of SC low-dose IL-2 therapy has appeared to enhance the efficacy of chemotherapy in advanced cancer patients with pre-treatment lymphocytopenia [44].

Finally, a perfectly complete personalization of cancer cure, which takes into consideration not only the biology, but also the psychological profile of cancer patients at both conscious and unconscious levels, would require a concomitant psychological evaluation through projective psychological tests, such as Rorschach test, since they cannot be manipulated by the rationality of patients [45].

The importance of the evaluation of the immune status of cancer patients in addition to the biological characteristics of tumor has been recently confirmed by several clinical studies, which have demonstrated that the simple evaluation of Lymphocyte-to-Monocyte Ratio [LMR], which reflects the interactions occurring between tumor and host immune system, may predict the prognosis of the neoplastic disease in terms of both response to therapy and survival time, since the evidence of abnormally low LMR value is associated with a poor prognosis, irrespectively of tumor histotype. Then, LMR could constitute a new simple inexpensive biomarker to monitor the clinical course of the neoplastic disease not only in relation to tumor characteristics, but also to the biological status of patients [46].

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