ORIGINAL ARTICLE

A Biological Approach with Targeted Therapies in Association with the Pineal Anti Cancer Immunomodulating Hormone Melatonin in Metastatic Solid Tumor Patients

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ABSTRACT

The recent introduction of targeted cancer therapy (TCT) has allowed the proposal of a more specific treatment of the neoplasms of each cancer patients. The inhibition of EGFR, VEGFR and BRAF activity represents the main target of treatment. However, the limit of the TCT is depending on the fact that it is generally proposed only in relation to the genetic features of tumours rather than on the immunobiological status of patients, which is fundamental in influencing the clinical efficacy of TCT itself. One of the fundamental endogenous biological response modifiers is the pineal hormone melatonin (MLT), which has also been proven to exert a direct anticancer action with an absolute absence of toxicity. On this basis, a study was planned with TCT in association with mild pharmacological doses of MLT (50 mg/day orally in the evening). TCT consisted of Sorafenib (n:2) or Sunitinib (n:1) in RCC, Erlotinib (n: 3), Gefitinib (n: 2) or Crizotinib (n: 1) in NSCLC, and Vemurafenib in melanoma (n: 5). A complete response (CR) was obtained in 3 patients (melanoma:1; NSCLC:1; RCC:1). Four other patients achieved a partial response (PR) (melanoma: 2; NSCLC: 2), while the remaining 7 patients had a disease stabilization (n: 3) or progression (n: 4). The median duration of response was 16 months. Patients who have an objective tumour regression (CR + PR) showed a significantly higher increase in LMR mean values. No important toxicity occurred. This preliminary study would suggest that the pineal hormone MLT may be successfully associated not only to cancer chemotherapy, but also to TCT to improve its efficacy and tolerability, by justifying further randomized clinical investigations.

Key words: BRAF, EGF, Lymphocyte-to-monocyte ratio, Melatonin, Pineal gland, Targeted cancer therapy, VEGF

INTRODUCTION

The discovery of oncogenes and tumor suppressor genes, and the complete characterization of human genome sequencing allowed a better knowledge of the mechanisms involved in tumor development and progression. Particularly, it has been shown that most of the more than hundred oncogenes known up to now encode protein tyrosine kinases, which act as receptors for tumor growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), or for angiogenic factors, such as vascular endothelial growth factor (VEGF) (1-4). EGF receptor (EGFR) and VEGF receptor (VEGFR)are involved in the simulation of cell proliferation and neo-angiogenesis, respectively (1-4). The somatic mutations responsible for the malignant transformation generally regard the pathways controlled by protein kinases, consisting of persistent activation, their over expression, small deletions of their regulatory regions, and loss of the autoinhibitory mechanisms of their activation. The enhanced protein kinase activation may be blocked by

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DOI: 10.33309/2639-8230.040202

specific neutralizing antibodies, or low molecular weight kinase inhibitors. Within the group of low molecular weight inhibitors, some of the main clinically employed drugs in the treatment of human metastatic solid tumours, the so-called targeted therapy, are represented by the VEGFR inhibitors Sunitinib and Sorafenib, the EGFR inhibitors Gefitinib and Erlotinib, the BRAF inhibitors Vemurafenib, Trametinib and Dabrafenib (5), and the multi-kinase inhibitor Regorafenib (6). Sunitinib and Sorafenib are used in the treatment of renal cell carcinoma (RCC) and hepatocellular carcinoma. EGFR inhibitors are particularly active in the treatment of non-small cell lung cancer (NSCLC), while BRAF inhibitors are effective in the treatment of melanoma. Finally, Regorafenib could be active in the treatment of several solid neoplasms, including colorectal cancer and glioblastoma (6). Finally, both NSCLC and lymphomas may respond to anaplastic lymphoma kinase (ALK) inhibitors, such as Crizotinib, Alectinib and Brigatinib (7). In any case, according to the recent discoveries in the area of Psycho-neuro-endocrine-immunology (PNEI), DNA expression has appeared to be physiologically under a central neuroendocrine control, mainly exerted by the pineal gland through the release of its indole hormone melatonin (MLT) (8), which plays a fundamental role in the regulation of the biological rhythms in relation to the light/dark photoperiod, including cell proliferation and the immune status. Several experimental and clinical studies have shown that MLT may exert a direct anticancer action (8, 9), due to several mechanisms, including a cytotoxic action (10), an anti-angiogenic activity (11) and an immunostimulatory effect on the anticancer immunity (12). Moreover, the concomitant administration of MLT may enhance the anticancer efficacy of several chemotherapeutic agents and reduce their toxicities (13, 14). On the contrary, only few experimental data are available about the possible influence of MLT on the targeted cancer therapy (TCT). In any case, in addition to its anticancer property, MLT could improve the efficacy of TCT by counteracting cancer cell genomic rearrangements and DNA repairing mechanisms (8, 9). On these bases, a preliminary phase 2 study was planned to evaluate the efficacy and tolerability of TCT in association with mild pharmacological doses of MLT.

MATERIALS AND METHODS

The study included 14 consecutive metastatic solid tumor patients (M/F: 11/3; median age: 61 years, range 39-71), who underwent TCT with low molecular weight kinase inhibitors. Eligibility criteria were, as follows: histologically proven metastatic solid tumour, measurable lesions, and low molecular weight kinase inhibitors as the first line therapy for the metastatic diseases. Solid neoplasms consisted of NSCLC in 6 (adenocarcinoma: 4; squamous cell carcinoma: 2), melanoma in 5 and RCC in the remaining 3 patients. Dominant metastasis sites were, as follows: nodes: 1; bone: 2; lung: 4; liver: 3; brain: 4. TCT at the conventional doses consisted of EGFR or ALK inhibitors (Erlotinib: 3; Gefitinib: 2; Crizotinib: 1) in NSCLC, VEGFR inhibitors (Sorafenib: 2; Sunitinib: 1) in RCC, and the BRAF inhibitor Vemurafenib in melanoma.After the ethical approval, the experimental protocol was explained to each patient, and written consent was obtained. MLT was given orally at 50 mg once/day in the dark period of the day, generally 30 minutes prior to sleep, corresponding to its physiological circadian light/dark rhythm (5), every day without interruption until disease progression. The clinical response was evaluated according to WHO criteria by repeating the radiological examinations, including CT, NMR and PET at 3 month-intervals. The biological response under therapy was clinically evaluated by determining the lymphocyte-to-monocyte ratio (LMR), because of its proven prognostic values, since a decline in LMR values has appeared to be associated with a lower survival and a low response to the conventional anticancer therapies (15). Normal values of LMR observed in our laboratory (95% confidence limits) were greater than 2.1. Data were statistically analysed by the chi-square test and the Student't test, as appropriate.

RESULTS

The clinical characteristics of patients and their response to therapy are reported in Table 1. The clinical response consisted of complete response (CR) in 3/14 (21%) patients (RCC: 1; NSCLC: 1; melanoma: 1), partial response (PR) in 4/14 (29%) (Melanoma: 2; NSCLC: 2), stable disease (SD) in 3(21%) (NSCLC: 2; RCC: 1) and progressive disease (PD) in 4 patients (29%) (Melanoma: 2; RCC: 1; NSCLC: 1). Then, a disease control (DC: CR + PR + SD) was achieved in 7/14 (50%) patients. The median duration of response was 16 months (range 11-34 months). The treatment was well tolerated in 13/14 patients, whereas only one patient with RCC, who had a PD on therapy, referred an important diarrhoea. No hematologic toxicity occurred. Lymphopenia occurred in only 2/14 (14%). On the contrary, LMR values increased on therapy, and LMR mean values achieved after three months of treatment in patients with objective tumour regression (CP + PR) was significantly higher than that observed in patients with SD or PD (3.5 /- 0.3 vs 2.0 +/- 0.4, mean +/- SE, $P<0.05$).

DISCUSSION

This preliminary clinical results show that a biological approach with low molecular weight kinase inhibitors,

including EGFR, VEGFR and BRAF inhibitors, in association with the antitumor immunomodulating pineal hormone MLT is a well tolerable and effective biotherapy of several solid tumour histotypes, including NSCLC, melanoma and RCC, also in patients with brain metastases. In more detail, the concomitant association with MLT would seem to prolong the duration of the clinical response with respect to the results reported in the literature with the only TCT. In fact, MLT could enhance the efficacy of TCT by either directly acting as an anticancer agent or reducing the genetic mutations of cancer cells (8-11), which are responsible for the resistance to TCT itself. Cancer progression has been proven to be characterized by a progressive decline in the nocturnal production of MLT, with a following loss of its light/dark circadian rhythm, and pineal hypofunction would represent one of the main endocrine cancer-related endocrine deficiencies (16, 17). Then, because of the influence of MLT on DNA expression, the endocrine pineal deficiency would furtherly contribute to the genetic mutations of cancer cells and to their resistance to the action of the anticancer drugs. Moreover, MLT could prolong the duration of TCT-induced clinical response by improving the status of the anticancer immunity, as suggested by the higher increase in LMR achieved in patients with an objective tumour regression with respect to those who had SD or PD. In fact, MLT has been shown to represent one of the main endogenous biological response modulator (12). In addition, it has recently been shown that the lack of efficacy of TCT and cancer immunotherapies may be due at least in part to an increased secretion of IL-17A (18), which may exert a direct stimulatory action on cancer growth and dissemination (19). MLT has been proven to inhibit IL-17 secretion (20), as well as the cannabinoid agents (21, 22). Therefore, MLT could improve the efficacy of TCT by opposing the possible increase in IL-17 endogenous production. The TCT is generally considered as a personalization of cancer cure. In the reality, however, it is not planned in relation to the personality of patients and their immunobiological status, but only in relation to tumour oncogenic characteristics and their histotypes. On the contrary, the concomitant administration of MLT or other similar biological agents could make more personalized the TCT, particularly by monitoring changes in immune status, as shown by the LMR, with the possibility to enhance MLT dosage in the presence of an evident decline in lymphocyte and increase in monocyte counts, because of MLT stimulatory effect onTh1 lymphocyte-induced secretion of IL-2 (12), which represent the main lymphocyte growth factor (23).

Table 1: Characteristics of cancer patients and their clinical response (WHO) to targeted therapy plus MLT.

n	SEX	AGE	TUMOUR	METASTASIS	TARGETED THERAPY	CLINICAL RESPONSE*
1	F	48	Renalcell carcinoma	Bone	Sorafenib	SD
2	F	66	Lung adenocarcinoma	Brain	Gefitinib	PR
3	M	58	Renal cell carcinoma	Liver	Sorafenib	PD
4	M	61	Melanoma	Brain	Vemurafenib	PD
5	M	64	Renalcell carcinoma	Lung	Sunitimib	CR
6	M	61	Melanoma	Brain	Vemurafenib	PR
7	M	41	Melanoma	Lung	Vemurafenib	CR
8	M	68	Lung adenocarcinoma	Brain	Erlotinib	CR
9	M	63	Melanoma	Nodes	Vemurafenib	PD
10	M	62	Melanoma	Liver	Vemurafenib	PR
11	F	59	Lung adenocarcinoma	Lung	Erlotinib	SD
12	M	65	Lung epidermoid cancer	Bone	Erlotinib	PD
13	M	39	Lung adenocarcinoma	Liver	Crisotinib	PR
14	M	71	Lung epidermoid cancer	Lung	Gefitinib	SD

CONCLUSION

In conclusion, the results of this preliminary phase 2 study may justify further randomized study with low molecular weight kinase inhibitors alone or in association with MLT in the treatment of metastatic solid neoplasms.

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How to cite this article: Lissoni P, Porro G, Messina G, Tomasi M, Fede G D. A Biological Approach with Targeted Therapies in Association with the Pineal Anti Cancer Immunomodulating Hormone Melatonin in Metastatic Solid Tumor Patients. J Clin Res Oncol 2022;4(2):10-13. DOI: 10.33309/2639-8230.040202