International Journal of Immunology and Immunobiology

Dose-Dependency of Antitumor Effects of the Pineal Hormone Melatonin in Untreatable Metastatic Solid Tumor Patients

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Abstract

Despite it is known since more than 50 years that the pineal hormone melatonin (MLT) may play an anticancer activity, as confirmed by several experimental and clinical studies, the clinical use of MLT in the treatment of cancer is still at the beginning. Most clinical studies have been performed with MLT dose of 20 mg/once daily in the dark period. Preliminary clinical studies with MLT in untreatable advanced cancer patients have demonstrated an inhibitory effect on tumor progression, with a prolonged 1-year survival. However, at present it is still unknown whether the antitumor action of MLT may be a dose-dependent event in human neoplasms. This preliminary study was performed to evaluate the dose-efficacy ratio of MLT in the treatment of human neoplasms. The study was performed in 14 consecutive metastatic solid tumor patients, for whom no other standard antitumor therapy was available. MLT was administered at a dose of 20 mg/day orally in the evening. In the case of progressive disease, MLT dose was progressively enhanced until 100 mg/day. MLT therapy at a dose of 20 mg/day induced a disease control in 7/145 patients, consisting of partial response (PR) in one patient and a stable disease (SD) in other 6 patients. After progression, dose increase of MLT until 100 mg induced again a SD in 6/14 (43%) and 1–year survival was achieved in 8/14 (56%). The results of this preliminary study would demonstrate that the antitumor activity of MLT may increase by increasing MLT dose, and then it seems to be a dose-dependent phenomenon.

Keywords

Melatonin; Dose-dependency; Cancer disease

Introduction

According to the criteria already established by Bartsch et al. [1], the pineal hormone melatonin (MLT) has been proven in experimental conditions to exert antitumor effects when it is given at pharmacological doses, corresponding to at least 20 mg/daily in humans, and during the only dark period of the day. The mechanisms of the anticancer activity of MLT are complex, but they have been almost completely defined, and they include both antiproliferative cytotoxic and immunomodulating effects [2-7]. The direct anticancer effects are consisting of induction of apoptosis of cancer cells, inhibition of epidermal growth factor receptor (EGF-R) activation, and prevention of intercellular junction alterations, which are responsible for changes in the intercellular matrix, that are the stimulus for tumor neo-.angiogenesis. The antitumor immune effects of MLT are consisting of stimulation of IL-2 secretion by T helper-1 (TH1) lymphocytes and IL-12 release from the dendritic cells. Finally, MLT has also been proven to exert anti-angiogenic effects, by representing the only known antitumor molecule existing in the nature capable of exerting the all three major mechanisms played by the common anticancer drugs, including the cytotoxic action, the anti.-angiogenic activity and the stimulation of the anticancer immunity [8]. At present, however, no study has been adequately performed in an attempt to establish whether the anticancer activity of MLT may be or not a dose-depending phenomenon, then whether its anticancer action may enhance by increasing its dosage. The possible increase in MLT anticancer action by enhancing its dosage could by justified by the fact that MLT may exert other anticancer effects rather than the only cytotoxic cytostatic effects, including its anti-angiogenic action and immuno-stimulatory activity. At present, most in human studies of MLT therapy of cancer have been performed at a dose of 20 mg/day orally during the dark period of the day [9]. The importance to establish whether the anticancer effect of MLT may be a dose-dependent phenomenon is clinically justified by the fact that MLT has no biological toxicity even though administered at doses greater more than 100 times with respect to the physiological ones [10]. Then, in the case of cancer progression under a dose of 20 mg/day, MLT dosage could be enhanced continuously until the end of the clinical history of patients with disseminated neoplasms, at least to stimulate their immune performance. This

Article Information

DOI: 10.31021/ijii.20181104
Article Type: Research Article
Journal Type: Open Access
Volume: 1 **Issue:** 1
Manuscript ID: IJII-1-104
Publisher: Boffin Access Limited

Received Date: 11 June, 2018
Accepted Date: 03 July, 2018
Published Date: 05 July, 2018

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Citation: Lissoni P, Messina G, Rovelli F, Brivio F, Di Fede G. Dose-Dependency of Antitumor Effects of the Pineal Hormone Melatonin in Untreatable Metastatic Solid Tumor Patients. Int J Immunol Immunobiol.2018 July;1(1):104

preliminary clinical study was performed in an attempt to evaluate the effects of an increase in MLT dosage on the clinical course of the neoplastic disease in a group of untreatable metastatic solid tumor patients because of lack of response to the previous conventional anticancer therapies, who had progressed under a palliative therapy with MLT at the classical dose of 20 mg/day.

Materials and Methods

The present preliminary phase 2 study included 14 consecutive cancer patients (M/F: 8/6; median age: 69 years, range 54-77; median performance status according to ECOG score: 1, range 0-3). Eligibility criteria were, as follows: histologically proven solid neoplasm, metastatic disease, measurable lesions, progression on previous chemotherapies, no availability of other standard anticancer treatments and life expectancy less than 1 year. Tumor histotypes were, as follows: colorectal cancer: 5; pancreatic adenocarcinoma: 4; lung adenocarcinoma: 3; biliary tract carcinoma: 1; gastric cancer: 1. Dominant metastasis sites were: nodes:1; lung:4; liver:3; liver plus lung:2; peritoneum:2; brain: 2. According to previous studies (9,10), MLT therapy was given at the beginning at a dose of 20 mg/day orally during the dark period every day without interruption, generally 30 minutes before sleeping. When patients showed a progression of disease, they underwent a program of escalation dose from 20 to 100 mg/day orally in the dark period progressively within 1 week, depending on the subjective tolerability of patients. Corticosteroids and opioid were used only in the presence of important symptoms, because of their immunosuppressive activity on the anticancer immunity. The clinical response was evaluated according to WHO criteria by repeating the radiological examinations, including CT scan, NMR and PET, as appropriate. Data were statistically evaluated by the chi-square test and the Student's t test, as appropriate.

Results

The clinical characteristics of patients and their clinical response to MLT therapy is reported in *Table 1*. The clinical response at the beginning of MLT therapy at a dose of 20 mg/die consisted of partial response (PR) in one patient with colon cancer and stable disease (SD) in 6 other patients (lung adenocarcinoma: 3; pancreatic adenocarcinoma:2; colon carcinoma: 1; gastric cancer:1. Then, a disease control (PR + SD) was achieved in 7/14 (50%) patients, whereas the remaining 7 patients had a progressive disease (PD) on MLT therapy at 20 mg/day. After progression under MLT at 20 mg/day, MLT therapy at a dose of 100 mg/day induced a SD in 6/14 (43%) patients (lung adenocarcinoma: 2; colon cancer: 2; gastric cancer: 1; pancreatic adenocarcinoma: 1), 6 of whom had already achieved a SD under MLT therapy at 20 mg/day, and no objective tumor regression, whereas the other 8 patients had a PD. Moreover, the percentage of SD obtained with MLT at 100 mg/day was significantly higher in patients, who achieved a SD or a PR under MLT at 20 mg/day than in those, who had a PD (5/7 vs. 1/7, $P< 0.05$). A survival longer than 1 year (*Fig 2*) was achieved in 8/14 (57%) patients, and the percent of 1-year survival was significantly higher in patients with disease control under MLT therapy than in those, who had a PD (6/6 vs. 2/8, $P< 0.05$). A survival longer than 1 year was obtained in 8/14 (56%) patients, and it was significantly higher in patients who achieved a SD under MLT at a dose of 100 mg than in those who had a PD (6/6 vs. 2/8, $P<0.01$). MLT-related biological toxicity occurred neither at 20, nor at 100 mg/day. A sleepness for only few days was observed in 3/14 (21%) under MLT therapy at 100 mg/day. On the contrary, MLT therapy improved the clinical status in most patients, with a benefit more evident in patients, who achieved a disease control on MLT therapy, and cachexia occurred in none of the patients treated with MLT.

Discussion

The results of this preliminary study, by showing the possibility to obtain a control the neoplastic progression by MLT therapy at 100 mg in patients, who had progressed under a dose of only 20 mg, would suggest that the antitumor activity of MLT in cancer patients may be a dose-dependent phenomenon, in agreement with the results previously observed in experimental conditions (1-7). This evidence would deserve important clinical implications in the treatment of human neoplasms, at least in terms of clinical status and survival, because of the lack of toxicity of MLT therapy and its very low social cost. Then, according to the results of this study, in future clinical investigations MLT therapy could already start at a dose of

N	Sex	Age	PS*	Tumor Metastases		Clinical Response**		Survival (Months)
				MLT 20 mg	MLT100 mg			
1	M	73	1	Lung	Lung	SD	SD	18
2	F	71	0	Pancreas	Nodes	SD	SD	15
3	M	74	2	Colon	Liver, Lung	PD	PD	8
4	F	59	0	Colon	Liver	PR	SD	28
5	M	72	1	Pancreas	Liver	PD	PD	14
6	M	77	1	Biliary tract	Lung	PD	PD	5
7	F	71	1	Colon	Lung	PD	SD	22
8	M	68	1	Pancreas	Liver, Lung	SD	PD	4
9	F	58	2	Stomach	Peritoneum	SD	SD	33
10	F	59	1	Lung	Lung	SD	SD	13
11	F	49	2	Lung	Brain, Lung	SD	PD	4
12	M	75	1	Pancreas	Liver, Lung	PD	PD	5
13	M	74	3	Colon	Brain, Liver, Lung	PD	PD	3
14	F	54	2	Rectum	Lung, Bone, Peritoneum	PD	PD	16

Table 1: Characteristics of patients and their clinical response (WHO)

* ECOG ; ** PR: Partial Response; SD: Stable Disease; PD: Progressive Disease

Patients	n	1-Year Survival
Overall Patients	14	8/14 (57%)
Responders	6	6/6 (100%) *
Non-responders	8	2/8 (25%)

Table 2: 1-year survival in metastatic cancer patients treated by high-dose MLT in relation to their clinical response.

* < 0.05 vs non-responders

100 mg/day, instead of 20 mg, as generally performed up to now (9), because of its apparent greater clinical antitumor efficacy on the clinical course of the neoplastic disease. Therefore, in future studies MLT therapy of human tumors would have to start at a dose of 100 mg/day or at a dose of at least 1 mg/kg b.w. Moreover, further studies in a great number of patients will be required to establish whether the antitumor activity of MLT in humans mainly depend on its effects on the antitumor immunity by investigating changes in cytokine secretion under MLT therapy, or on the expression of MLT receptors by tumor cells.

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