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Endocrine and Immune Effects of Melatonin Therapy in Metastatic Cancer Patients

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Abstract—*Melatonin, the most important indole hormone produced by the pineal gland, appears to inhibit tumor growth; moreover, altered melatonin secretion has been reported in cancer patients. Despite these data, the possible use of melatonin in human neoplasms remains to be established. The aim of this clinical trial was to evaluate the therapeutic, immunological and endocrine effects of melatonin in patients with metastatic solid tumor, who did not respond to standard therapies. The study was carried out on* 14 *cancer patients (colon, six; lung, three; pancreas, two; liver, two; stomach, one). Melatonin was given intramuscularly at a daily dose of* 20 mg *at* 3.00 *p.m., followed by a maintenance period in an oral dose of* 10 mg *daily in patients who had a remission, stable disease or an improvement in PS. Before and after the first* 2 *months of therapy, GH, somatomedin-C, beta-endorphin, melatonin blood levels and lymphocyte subpopulations were evaluated. A partial response was achieved in one case with cancer of the pancreas, with a duration of* 18+ *months; moreover, six patients had stable disease, while the other eight progressed. An evident improvement in PS was obtained in* 8/14 *patients. In patients who did not progress, T4/T8 mean ratio was significantly higher after than before melatonin therapy, while it decreased in patients who progressed. On the contrary, hormonal levels were not affected by melatonin administration.*

This study would suggest that melatonin may be of value in untreatable metastatic cancer patients, particularly in improving their PS and quality of life; moreover, based on its effects on the immune system, melatonin could be tested in association with other antitumor treatments.

INTRODUCTION

IN THE last 10 years, several experimental observations have demonstrated that the neuroendocrine system can influence tumor growth [1–8] through the release of a great variety of neurohormones. This finding could lead in the future to a neuroendocrine approach in the treatment of cancer, and to more detailed knowledge of the biochemical basis by which psychoemotional factors seem to influence the neoplastic development.

Among neuropeptides involved in the control of cancer growth, enkephalins have been shown to play an important role, since they appear to be able to inhibit tumor development in several experimental conditions [9]. In addition to recent evidence, it must be noted that it has been known for many years that the pineal gland is involved in the regulation of cancer development [10–14]. Pinealectomy stimulates tumor growth [10–12], while melatonin, its main hormone, has been shown either to counteract the pinealectomy-induced tumor stimulation [13], or to induce a tumor regression in animals [14].

Experimental evidence would suggest that melatonin plays an antineoplastic activity through several mechanisms, including a stimulation of the immune system [15, 16], an inhibition of the secretion of growth factors [17] and a possible differentiating effect on cancer cells [18], rather than exerting a direct cytotoxic activity against neoplastic cells. In particular, the effects of melatonin on the immune system have to be taken into consideration since it has been demonstrated that the pineal hormone is important in maintaining an optimal immune performance [15]. In contrast, no data are available at the present time about the possible action of melatonin on oncogene expression.

Based on the well documented anomalies of melatonin secretion in oncologic patients [19–21], it is possible to suggest that some endocrine, metabolic and immune dysfunctions, which may characterize cancer patients, may at least be related to the anomalous pineal function.

Despite the well documented antineoplastic

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activity of the pineal hormone in animals and the absence of toxicity in humans [22], only a few studies have been made until now to investigate melatonin action in cancer patients [23–25].

The present study was carried out to draw some preliminary conclusions about the biological effects of melatonin in patients with metastatic solid neoplasms, who did not respond to standard antitumor treatments or for whom no effective therapy is available.

MATERIALS AND METHODS

From September 1986 to August 1987, 14 consecutive cancer patients of both sexes (nine men and five women), with a median age of 59 years (range 45–74), followed in the Medical Oncology Branch of the Radiation Oncology Division of San Gerardo Hospital of Monza, entered the study.

Criteria for eligibility were as follows: (1) histologically proven neoplastic disease; (2) measurable neoplastic lesions; (3) failure to respond to standard antitumor treatment, or cancers for which no effective therapies are available; (4) Karnofsky status of 30–100%, and a life expectancy greater than 6 months; (5) no other anticancer therapy for at least 30 days prior to start of melatonin administration; (6) no concomitant chronic treatment with opioids, steroids or other hormones; (7) informed consent.

Cancer types were: colon, six; lung, three; pancreas, two; liver, two; stomach, one. All patients had metastatic disease. Nine patients had been previously treated with surgery and/or chemotherapy, while the other five were not treated, since they refused chemotherapy. All patients previously treated with antiblastic drugs had rapidly progressed during chemotherapy, as shown by the increase of at least 30% of the neoplastic lesions every two months, and/or by the appearance of new lesions within the last 2 months prior to melatonin therapy. In patients pretreated with chemotherapy the study was started after a median interval of 3 months (range 1–5) from the last cycle of chemotherapy. No patients received prior radiation therapy.

Patients were treated with melatonin at a dose of 20 mg daily intramuscularly. We chose to give melatonin at high doses, since it has appeared to induce tumor regression in animals only at pharmacological dosages [14]. Moreover, the pineal hormone was given intramuscularly for 2 months, to guarantee a more reliable absorption. In addition it was administered at 3.00 p.m., since it had been reported that the biological effects of the exogenous melatonin are more pronounced in the afternoon than in the morning [26], and that its antineoplastic activity in animals is at a maximum during the afternoon [27].

This induction phase of 2 months was followed in responding patients, in those who achieved a stable disease or an improvement of performance status (PS), by a maintenance period, during which melatonin was given orally for better acceptance by patients, at a daily dose of 10 mg, following a time schedule selected for pharmacologically reproducing the physiological light/dark rhythm of the pineal hormone (8.00 a.m.: 2 mg; 3.00 p.m.: 2 mg; 10.00 p.m.: 6 mg). Melatonin was supplied by Biosynth A.G. (Staad, Switzerland).

Clinical response was graded as follows: complete response (CR) was the disappearance of all evidence of tumor for at least 1 month; partial response (PR) was a reduction more than 50% of the product of the longest perpendicular diameters of all neoplastic lesions for at least 1 month; stable disease (SD) showed no objective decrease or increase in tumor measurements; progressive disease (PD) was an increase by more than 25% in the product of the longest perpendicular diameters of lesions, or the appearance of new lesions.

To evaluate the neoplastic lesions, radiological examinations were repeated every 2 months. Moreover, to exclude propensive disease elsewhere, chest radiography or CT scan, and abdominal echotomography or CT scan were also repeated every 2 months. Routine laboratory tests were made every 15 days for the first 2 months, then every month. At the same intervals, electrocardiograms were also repeated, because of the evidence of electrocardiographic modifications following melatonin administration in rats (Biella *et al.*, personal communication).

To evaluate hormonal and immune functions, venous blood samples were drawn from each patient at 9.00 a.m., either before or 2 months after the start of melatonin therapy. In two patients only (cases 8 and 10), who rapidly worsened, the control was repeated in advance, after 44 and 23 days, respectively. Melatonin and GH serum levels, somatomedin-C and beta-endorphin plasma concentrations, and lymphocyte subpopulations were analyzed in each blood sample. For endocrine determinations, serum and plasma were obtained by centrifugation, and stored at −20°C until tested. Hormonal level were determined by the RIA method, using commercially available kits (Sclavo, Siena, Italy for GH; Nichols Institute Diagnostics, St. Juan Capistrano, California, U.S.A. for somatomedin-C and beta-enodorphin; Euro-Diagnostics, Apeldoorn, Holland for melatonin). Intraassay and interassay coefficients of variation were 3% and 5% for GH, 3% and 7% for somatomedin-C, 4% and 7% for beta-endorphin, and 6% and 10% for melatonin, respectively. Hormonal values were considered within the normal range in our laboratory when they were: GH <5 ng/ml; somatomedin-C <2 U/ml; beta-endorphin <120 pg/ml; melatonin

<28 pg/ml. For immune detection, peripheral mononuclear cells were isolated from heparinized blood samples with Ficoll-Hypaque density gradients. B lymphocytes (B), total T lymphocytes (T3), T helper/inducer (T4) and T suppressor/cytotoxic (T8) percentages were detected with a flow cytometer using monoclonal antibodies supplied by Ortho Diagnostics (Raritan, NJ). Moreover, T4/T8 ratio was determined in each patient. Normal values were as follows: T3 >70%, B <19%, T4 >40%, T8 <35%, T4/T8 ratio >1.2.

Results are reported as mean ± S.D., and data were analyzed by Student's *t* test or chi-square test, as appropriate.

RESULTS

Characteristics of cancer patients and their clinical response after the 2 months of melatonin administration are reported in Table 1. No metabolic, hematologic, renal, hepatic, cardiac and nervous toxicities were seen during melatonin treatment. Electrocardiograms were also not influenced. Moreover, no undesirable subjective effects were observed; on the contrary, most patients reported relaxation during melatonin treatment, and a mild heaviness in the legs in some cases for a few minutes after drug injection.

No progression was observed in 6/14 cancer patients (43%) after the 2 months of therapy. An objective tumor regression higher than 50% was seen in 1/14 only (7%); he was affected by head of pancreas carcinoma, as diagnosed at explorative laparotomy, with left supraclavear node involvement; after 2 months of melatonin, a complete regression of the primary tumor was achieved, as shown by CT scan, while lymph node dimensions remained substantially unchanged. Five other patients (colon: two; lung: two; liver: one), four of whom had been previously treated with chemotherapy and had rapidly progressed during the chemotherapeutic treatment, showed a stabilization of the disease. All patients with response or stable disease had a mild or evident improvement in their PS. The last eight patients (57%) progressed during melatonin therapy; despite tumor progression, two of whom, both suffering from colon cancer, had a clear amelioration of PS, while two others, the first with hepatocarcinoma and the second with a very disseminated lung adenocarcinoma died before concluding the 2 months of melatonin therapy, after 38 and 29 days, respectively. In summary, PS score increased under melatonin in 8/14 cancer patients (57%).

Hormonal and immune evaluations are listed in Tables 2 and 3, respectively. Before therapy, high levels of melatonin were observed in three cases (21%). GH and somatomedin-C values were elevated in two (14%) and three (21%) patients, respectively, while those of beta-endorphin were within the normal range in all cases. After the 2 months of melatonin administration, GH, somatomedin-C and beta-endorphin mean concentrations showed no significant differences with respect to those seen before therapy. The only melatonin mean levels were obviously significantly higher after than before the exogenous administration of the pineal hormone ($P < 0.001$). Moreover, no differences were seen in melatonin mean values before treatment between patients who progressed and those who did not progress during the hormonal treatment. Similarly, basal mean concentrations of GH, somatomedin-C and beta-endorphin in patients with progression were not significantly different with respect to those detected in patients who had no progression; after therapy, the GH mean values were only higher in patients who progressed than in the other group,

Table 1. *Clinical data of cancer patients and their response to melatonin treatment*

Cases	Sex	Age (years)	Tumor	Histology	Sites of metastasis	Previous therapies*	Clinical response†	Duration of response (months)	PS (Karnofsky) Before	After
1	M	58	Colon	Adenocarcinoma	Liver, lung	Surgery, 5-FU/FA	PD	—	40	90
2	M	62	Colon	Adenocarcinoma	Liver	Surgery, 5-FU/FA	PD	—	40	60
3	M	74	Lung	Epidermoid	Lung, bone	CDDP/VP-16	SD	5	40	80
4	F	66	Colon	Adenocarcinoma	Lung	Surgery, 5-FU/FA	PD	—	40	40
5	F	65	Pancreas	Adenocarcinoma	Liver	—	PD	—	30	20
6	M	58	Pancreas	Adenocarcinoma	Nodes	—	PR	18+	30	100
7	F	43	Colon	Adenocarcinoma	Lung, liver, bone	Surgery, 5-FU/FA	SD	2	50	60
8	M	72	Liver	Hepatocarcinoma	Lung	CDDP/VP-16	PD	—	30	0
9	M	68	Lung	Adenocarcinoma	Bone	CDDP/VP-16	SD	6	30	50
10	M	52	Lung	Adenocarcinoma	Lung, liver, adrenal, pancreas, bone, skin	—	PD	—	30	0
11	M	54	Liver	Hepatocarcinoma	Lung	—	SD	3	30	40
12	M	57	Stomach	Adenocarcinoma	Liver	—	PD	—	30	20
13	F	59	Colon	Adenocarcinoma	Liver, lung	Surgery, 5-FU/FA	PD	—	40	30
14	F	45	Colon	Adenocarcinoma	Liver, spleen, pelvis	Surgery, 5-FU/FA	SD	3	40	60

*5-FU/FA: fluorouracil, folinic acid; CDDP/VP-16: *cis*-platinum, etoposide.
†PR: Partial response; SD: stable disease; PD: progressive disease.

Table 2. Individual and mean hormonal blood levels before and after 2 months of melatonin treatment in 14 advanced cancer patients

Cases	Melatonin (pg/ml)		Beta-endorphin (pg/ml)		GH (ng/ml)		Somatomedin-C (U/ml)	
	Before	After	Before	After	Before	After	Before	After
1	15	67	22	29	5.4	1.8	0.6	1.1
2	14	64	21	18	5.6	5.9	2.9	0.9
3	12	99	22	36	1.2	2.2	0.7	0.4
4	11	214	20	13	0.5	8.3	0.4	0.3
5	13	59	17	19	2.6	3.1	1.0	1.3
6	8	37	19	12	0.2	0.2	2.1	0.8
7	27	78	31	28	1.3	0.9	1.2	1.1
8*	29	96	11	15	2.9	2.7	0.3	0.4
9	33	83	12	17	1.1	1.2	1.0	0.9
10†	22	72	11	13	0.6	1.4	0.8	1.5
11	33	104	34	28	3.8	2.7	0.9	1.3
12	21	79	23	25	1.4	1.1	1.1	0.8
13	16	88	18	21	0.9	1.1	2.3	2.4
14	18	66	26	24	1.5	1.7	1.3	1.6
$\bar{x}$	19	86	20	21	2.1	2.4	1.2	1.1
± S.D.	8	41	7	7	1.7	2.1	0.7	0.6

*After 44 days.
†After 23 days.

Table 3. Immunological effects of 2 months of melatonin treatment in 14 advanced cancer patients

Cases	Leukocyte count (%)												Lymphocyte subpopulations (%)									
	Before						After						Before					After				
	WBC	N	E	B	L	M	WBC	N	E	B	L	M	T3	B	T4	T8	T4/T8	T3	B	T4	T8	T4/T8
1	4500	55	6	0	35	4	6400	75	3	0	21	1	74	17	49	34	1.4	67	20	40	25	1.6
2	4900	49	9	0	33	9	6700	69	4	0	25	2	72	20	47	22	2.1	75	17	51	23	2.2
3	10,40	80	2	0	11	7	9400	79	3	0	18	0	71	14	42	26	1.6	72	12	45	26	1.7
4	0	66	3	0	31	0	9500	65	3	0	32	0	65	28	37	28	1.3	61	29	24	35	0.7
5	600	63	3	0	31	3	7100	72	2	0	24	2	68	15	48	22	2.1	66	12	28	37	0.8
6	4800	64	1	0	34	1	6900	63	1	0	36	0	66	12	29	36	0.8	67	18	46	18	2.6
7	5300	70	0	0	27	3	9100	65	2	0	30	3	75	18	41	28	1.5	76	16	43	26	1.7
	3800																					
8*	8000	71	1	0	22	6	7200	76	2	0	17	5	78	13	17	57	0.3	68	21	13	56	0.2
9	11,00	65	1	0	33	1	7300	62	2	0	36	2	54	15	23	37	0.6	71	8	38	24	1.6
10†	0	78	3	0	16	3	9400	83	1	0	13	3	71	16	44	26	1.7	58	15	25	32	0.8
11	8300	67	1	0	30	2	11,40	71	1	0	27	1	66	21	27	37	0.7	64	11	42	20	2.1
12	8900	74	3	0	22	1	0	84	1	0	10	5	73	32	47	25	1.9	67	33	24	36	0.7
13	10,50	61	3	0	32	4	12,10	55	1	0	42	2	81	17	44	32	1.4	78	15	35	37	0.9
14	0	63	2	0	31	4	0	61	2	0	35	2	83	18	46	38	1.2	84	16	49	29	1.7
	7300						8400															
	4800						8000															
$\bar{x}$	7000	66	3	0	29	3	8500	70	2	0	26	2	71	18	39	32	1.3	70	17	36	30	1.4
± S.D.	2500	8	2		7	2	1700	9	1		10	1	7	6	10	9	0.5	7	7	11	10	0.7

*After 44 days.
†After 23 days.

without, however, any significant difference.

As far as immune parameters are concerned, an inverted T4/T8 ratio was observed before treatment in 4/14 cancer patients (28.5%). T4 and T8 percentages were respectively reduced and enhanced in 5/14 cases (36%), and in four patients there was an association between low T4 and high T8 values. In one patient only there was a low percentage of T3 lymphocytes (7%), while B cells were elevated in 4/14 cases (28.5%). Melatonin treatment did not induce significant changes in leukocyte count. Similarly, both lymphocyte subpopulation mean percentages and T4/T8 mean ratio after treatment were not significantly different from those observed before. Nevertheless, by evaluating changes in lymphocyte subgroups in relation to the clinical

response, different behavior was observed between patients with or with no progression. In patients who did not progress, the T4/T8 mean ratio was significantly higher after than before melatonin treatment ($P < 0.05$); an increase greater than 30% with respect to that observed before therapy was achieved in 4/6 patients who had not progressed, and a normalization of T4/T8 ratio was obtained in all three patients who showed an inverted ratio before therapy, while in none of these patients was a reduced T4/T8 ratio observed. Moreover, T4 and T8 percentages were respectively higher and lower after than before melatonin treatment, without, however, significant differences. On the contrary, a decrease of T4/T8 ratio greater than 30% was found after melatonin treatment in 6/8 (75%) patients who progressed during the hormonal treatment; in these patients, T4/T8 mean ratio was lower after than before treatment, but this difference was not statistically significant. The percentage of decrease of T4/T8 ratio was significantly higher in patients who progressed than in those with response or stable disease (6/8 vs. 0/6; $P < 0.01$). Finally, the T4/T8 mean ratio observed after melatonin treatment was significantly higher in patients who showed no progression than in those who progressed ($P < 0.025$). T4 and T8 mean percentages were respectively higher and lower in patients who did not progress than in those who did, without, however, significant differences.

Hormonal and immune mean values observed in patients with or without progression are reported in Table 4.

DISCUSSION

These preliminary results concerning the employment of the pineal hormone in the therapy of advanced untreatable human neoplasms would seem to suggest that melatonin may be able to slow tumor growth, since stable diseases and one objective tumor regression were achieved in some cancer patients who had rapidly progressed under standard chemotherapeutic treatments or had cancers for which there were not effective therapies. Moreover, despite tumor progression, melatonin treatment appeared to improve the performance status and the quality of life in a percentage of cancer patients, without determining any side-effect.

The mechanisms by which melatonin would seem to counteract cancer growth are still obscure. Based on these results, it appears that the antineoplastic activity exerted by melatonin is not mediated by an inhibited secretion of hormones involved in the regulation of cell proliferation, such as GH, somatomedin-C and beta-endorphin. In particular, our results disagree with those reported by Starr [23], who described a therapeutic effectiveness of the pineal indole in the only cancer patient with high GH levels before the start of treatment. Nevertheless, these results cannot allow us to draw definite conclusions about the effects of melatonin on growth factor secretions, sinc they are limited to GH and somatomedin-C detection; further studies, in an attempt to evaluate the relation between the pineal indole and other growth factors, which have been seen to play an important role in the stimulation of tumor development, such as PDGF, EGF and TGF, and its influence on growth factor receptors and oncogene expression, will be needed to establish whether or not melatonin may affect tumor growth by modulating the mechanisms involved in the control of cell proliferation.

As far as the effect on immunity is concerned, this study demonstrates that the effectiveness of melatonin in slowing-down tumor growth is associ-

Table 4. Immune and hormonal values (mean ± S.D.) in cancer patients before and after 2 months of melatonin treatment in relation to their clinical response

	Patients with progression ($n = 8$)		Patients without progression ($n = 6$)	
	Before	After	Before	After
Hormones				
Melatonin (pg/ml)	18 ± 6	92 ± 51*	22 ± 11	78 ± 24*
GH (ng/ml)	2.4 ± 2.0	3.2 ± 2.6	1.5 ± 1.2	1.6 ± 0.8
Somatomedin-C (U/ml)	1.2 ± 0.9	1.1 ± 0.7	1.2 ± 0.5	1.0 ± 0.4
Beta-endorphin (pg/ml)	18 ± 5	19 ± 6	24 ± 8	24 ± 9
Lymphocytes (%)				
T3	73 ± 5	67 ± 7	69 ± 10	72 ± 7
B	19 ± 7	20 ± 7	16 ± 3	14 ± 4
T4	42 ± 11	30 ± 12	35 ± 9	44 ± 4
T8	31 ± 11	35 ± 10	34 ± 5	25 ± 6
T4/T8	1.5 ± 0.6	0.9 ± 0.6	1.1 ± 0.4	1.9 ± 0.4†

*$P < 0.001$ vs. before treatment.

†$P < 0.05$ vs. before treatment; $P < 0.025$ vs. patients with progression.

ated with an improvement in the immune parameters, because of the evidence of the normalization of T4/T8 ratio in patients who had control of their disease, while neither antitumor effect nor an improvement in PS score were observed in patients whose immune disorders were not corrected by melatonin therapy. These results, however, do not allow us to affirm that the improvement in immune parameters can depend on a direct action of melatonin, since the possible influence of other factors, including the amelioration of the quality of life and the nutritional status, cannot be excluded. Moreover, to further clarify what effect melatonin has on the immune system, other important immunological functions must be investigated, particularly interlerleukin-2 production, which is often reduced in patients with disseminated cancer [28], and the generation of lymphokine-activated killer cells (LAK) [29]. Anyhow, the association between melatonin effectiveness and the normalization of T helper/suppressor ratio has to be taken into consideration, particularly in cancer immunotherapy, also on the basis of the demonstrated neuroimmunomodulatory activity of melatonin [15]. In fact, it is known that the failure of immunotherapy of tumors may result in part from the capacity of conventional immunotherapeutic agents to activate suppressor cells [30], as well as host cells involved in inhibiting tumor proliferation, and at present no effective therapies are available to antagonize the generation of suppressor cells. This study, by showing that melatonin therapy can be associated with an increase in T4/T8 ratio, could suggest that the pineal hormone may be useful to correct immune disorders in cancer patients, both in basal conditions and after antitumor therapies.

In conclusion, melatonin seems to play a role in regulating host biological reactions against cancer; rather than to be active alone in the treatment of tumors, it could be employed to potentiate the effectiveness of other anticancer therapies. Therefore, further studies, carried out on a greater and a more homogeneous case-series of cancer patients, by administering melatonin alone or in association with other antitumor treatments, including chemotherapy and the immunotherapy with LAK cells and interleukin-2, will be required to establish the exact role of the pineal hormone in the treatment of human neoplasms.

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