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Is there a role for melatonin in supportive care?

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Abstract Melatonin (MLT) is the main hormone released from the pineal gland and has proved to have physiological antitumor activity. MLT has been shown to exert anticancer activity through several biological mechanisms: antiproliferative action, stimulation of anticancer immunity, modulation of oncogene expression, and anti-inflammatory, anti-oxidant and anti-angiogenic effects. Several experimental studies have shown that MLT may inhibit cancer cell growth, and preliminary clinical studies seem to confirm its anticancer property in humans. In addition, MLT may have other biological effects, which could be useful in the palliative therapy of cancer, namely anticachectic, anti-asthenic and thrombopoietic activities. On this basis, the present clinical investigation was performed in an attempt at better definition of the therapeutic properties of MLT in human neoplasms. In a first clinical study, we evaluated the effects of MLT in a group of 1,440 patients with untreatable advanced solid tumors, who received supportive care alone or supportive care plus MLT. In a second study, we evaluated the influence of MLT on the efficacy and toxicity of chemotherapy in a group of 200 metastatic patients with chemotherapy-resistant tumor histotype, who were randomized to receive chemotherapy alone or chemotherapy plus MLT. In both studies, MLT was given

orally at 20 mg/day during the dark period of the day. The frequency of cachexia, asthenia, thrombocytopenia and lymphocytopenia was significantly lower in patients treated with MLT than in those who received supportive care alone. Moreover, the percentage of patients with disease stabilization and the percentage 1-year survival were both significantly higher in patients concomitantly treated with MLT than in those treated with supportive care alone. The objective tumor response rate was significantly higher in patients treated with chemotherapy plus MLT than in those treated with chemotherapy alone. Moreover, MLT induced a significant decline in the frequency of chemotherapy-induced asthenia, thrombocytopenia, stomatitis, cardiotoxicity and neurotoxicity. These clinical results demonstrate that the pineal hormone MLT may be successfully administered in medical oncology in the supportive care of untreatable advanced cancer patients and for the prevention of chemotherapy-induced toxicity.

Keywords Cancer · Cachexia · Melatonin · Pineal gland · Supportive care

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Introduction

Melatonin (MLT), an indole molecule, cannot be considered simply as a pharmacological drug, since it is an endogenous endocrine substance consisting of the best known hormone released from the pineal gland, one of the seven major human endocrine glands, whose physiology remained obscure until a few years ago [5]. Experimental studies have demonstrated that the pineal gland has several modulatory biological functions, which suggests that the physiological significance of the pineal is that of a central regulator of the immunoneuroendocrine interactions in relation to either the endogenous homeostasis or universal information, namely the light/dark photoperiod and magnetic fields [3, 10]. Most of the endocrine glands, in particular the gonads, adrenal and hypophysis, release hormones that are potentially able to promote cancer cell proliferation. In contrast, the pineal seems to be the only endocrine gland that has a physiological predominantly anticancer role through the circadian release of several potentially antitumor indole and peptidergic hormones [1, 4], the best known of which is MLT [5]. Moreover, several clinical studies have demonstrated that cancer progression is associated with a progressive decline in the pineal function and in MLT secretion, mainly during the dark period of the day [11]. Therefore, diminished nocturnal secretion of MLT would be a very common cancer progression-associated endocrine deficiency. In addition, since MLT may

have an anticancer activity [4, 5, 19], its progressive decline with cancer progression could play a part in the clinical course of the neoplastic disease. From this point of view, the first significance of MLT therapy in advanced cancer patients is that of the classic endocrine replacement treatment of cancer progression-related pineal deficiency. The other biological mechanisms justifying MLT administration in medical oncology as a possible new natural anticancer agent consist in antiproliferative activity [8], immunostimulatory effect on anticancer immunity, namely IL-2 production [18], modulation of oncogene expression [6], anti-oxidant activity [20], thrombopoietic action [7], psychomimetic properties, namely anti-anxiety, antidepressant and anti-asthenic effects [1], and an anticachectic property attributable to the inhibition of TNF alpha secretion [22].

The main rationale for MLT application in cancer patients is summarized in Table 1. Moreover, because of its anti-oxidant and hematopoietic activities [7, 16, 20], MLT could be effective in the modulation of cancer chemotherapy, as shown in Table 2. In more detail, MLT has been proven to prevent chemotherapy-induced lymphocyte damage [18]. Therefore, since the immune status appears to influence the prognosis of cancer patients [2], MLT-induced prevention of chemotherapy-related immunosuppression could have a prognostic impact, mainly on the survival time and on the quality of life. Experimental studies have already demonstrated that pharmacological

Table 1 Rationale for administration of melatonin in medical oncology

1. Endocrine replacement therapy of cancer progression-related decline in pineal function	
2. Anticancer activity of melatonin	<p>Direct cytotoxic or cytostatic effect (breast cancer, prostate cancer, gliomas, melanoma, pancreatic cancer, hepatocarcinoma, lung cancer)</p> <p>Immunomodulatory effects (stimulation of IL-2 secretion and activity)</p> <p>Cytodifferentiating activity (by modulating oncogene and endocrine receptor expression)</p> <p>Anti-inflammatory effects (by inhibiting the secretion of inflammatory, immunosuppressive cytokines, such as IL-6)</p> <p>Anti-angiogenic activity (by inhibiting VEGF secretion)</p>
3. Palliative therapy	<p>Neoplastic cachexia</p> <p>Depression and asthenia</p> <p>Thrombocytopenia</p>

Table 2 Rationale for melatonin–chemotherapy (CT) association in cancer treatment

Increased efficacy	<p>Prevention of CT-induced lymphocyte damage with potential increased survival</p> <p>Anti-oxidant-induced increase in cytotoxic activity of CT and possible enhancement of tumor response rate</p>
Prevention of toxicity	<p>Thrombocytopenia</p> <p>Neurotoxicity</p> <p>Cardiotoxicity</p> <p>Immunosuppression-related symptoms</p> <p>Asthenia</p>

doses of MLT given during the dark period of the day are required to achieve its maximal therapeutic antitumor efficacy in terms of cancer growth and cancer-related symptoms [4, 5]. Moreover, the period of the day in which MLT is administered appears to have a greater influence on its antitumor activity than does its dosage. In fact, no clear dose–response relation in MLT efficacy has been documented [22], whereas administration of MLT during the light period of the day has been shown not to be followed by any relevant anticancer activity [4, 5].

Previous preliminary clinical studies in cancer patients have already shown the efficacy of MLT in the treatment of cancer-related cachexia [13, 21] and thrombocytopenia [16]. Moreover, MLT appears to induce stabilization of disease in metastatic cancer patients progressing during classic anticancer therapies [12]. Finally, MLT has been shown to reduce the toxicity of chemotherapy and enhance its therapeutic efficacy in advanced cancer patients with poor clinical status, which is then probably characterized by an effective endogenous MLT deficiency [15]. On this basis, the present study was performed with the aim of defining the role of MLT in the supportive care of patients with neoplasms more closely.

Materials and methods

In a first clinical study, we evaluated the efficacy of MLT in 1,440 patients with untreatable advanced solid tumors who had not responded to previous standard anticancer therapies and for whom no other effective conventional treatment was available. According to tumor histotype, patients were randomized to receive supportive care alone or supportive care plus MLT. Eligibility criteria were as follows: histologically confirmed solid tumor, at least one previous cycle of chemotherapy, no double tumor, and no previous biological therapy other than MLT.

In a second clinical study, we evaluated the efficacy of concomitant MLT administration on chemotherapy-induced toxicity and therapeutic activity in 200 previously untreated patients with metastatic solid tumors who had chemotherapy-resistant cancer and a good clinical status. According to the chemotherapeutic regimen, patients were randomized to receive chemotherapy alone or chemotherapy plus MLT. Eligibility criteria were as follows: histologically confirmed metastatic solid tumor resistant to chemotherapy, including non-small-cell lung cancer, colorectal cancer, gastric cancer and soft tissue sarcomas, no previous chemotherapy for the metastatic disease, no double tumor, good clinical status [performance status (Karnofsky) greater than 80%], and no concomitant biological therapy other than MLT.

The experimental protocols were explained to each patient, and written consent was obtained. The clinical response and toxicity were evaluated according to WHO criteria, by repeating the radiological examinations every 2 months. Asthenia, anorexia and mood were assessed by means of a specific patient report. Data were statistically analyzed by the Chi-square test. Moreover, the survival curves were plotted according to the Kaplan-Meier method, and the differences between curves were evaluated by the log-rank test.

MLT was supplied by Helsinn Chemicals (Biasca, Switzerland). According to our previous studies [12, 13, 15, 16], MLT was given orally at 20 mg/day during the dark period of the day, every day for at least 2 months. In patients treated with chemotherapy, MLT was also given every day without interruption until disease progression, starting few days before the start of chemo-

therapy. The supportive care was the same in both groups of patients, consisting of opioids and anti-inflammatory nonsteroidal drugs. Corticosteroids were acutely used only for clinical reasons.

Results

The clinical characteristics of patients are reported in Tables 3 and 4. As shown, the two groups of patients in both studies were well matched for the main prognostic variables, including tumor histotype, dominant sites of metastasis, clinical status, and age.

Table 5 shows the results obtained in untreatable advanced cancer patients who received supportive care alone or supportive care plus MLT. No complete response

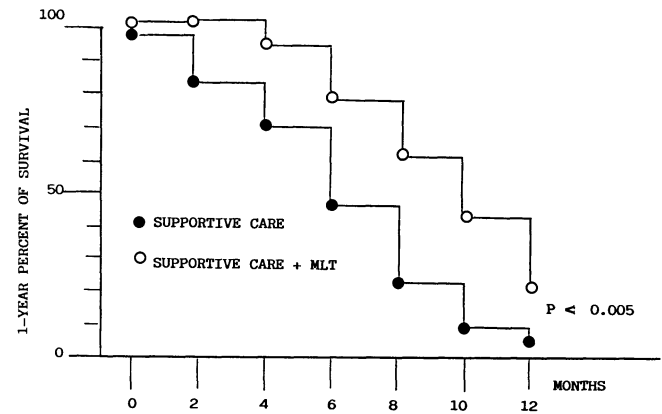
Table 3 Clinical characteristics of 1,440 advanced untreatable solid tumor patients treated with melatonin (MLT) plus supportive care or supportive care alone (PS performance status)

Characteristics	Supportive care	Supportive care+MLT
<i>N</i>	718	722
M/F	406/312	402/320
Median age (years)	65 (36–84)	66 (39–86)
Median PS (Karnofsky)	60 (40–90)	60 (30–100)
Metastatic disease	700/718	701/722
Tumor histotype		
<i>Lung cancer</i>	192	194
Non-small-cell	180	183
Small-cell	12	11
<i>Gastrointestinal tract</i>	279	283
Colorectal cancer	137	142
Gastric cancer	50	48
Pancreatic cancer	35	38
Hepatocarcinoma	17	19
Biliary tract cancer	40	36
<i>Endocrine-dependent tumors</i>	77	77
Breast cancer	60	58
Prostate cancer	17	19
<i>Gynecologic tumors</i>	31	30
Ovarian cancer	11	9
Cervix cancer	13	14
Endometrial cancer	7	7
<i>Miscellaneous</i>	139	138
Renal cell cancer	26	28
Bladder cancer	6	6
Testis cancer	7	6
Melanoma	41	37
Soft tissue sarcoma	21	19
Head and neck cancer	20	21
Brain glioblastoma	18	21
Dominant metastasis sites		
Soft tissues	46	44
Bone	82	83
Lung	394	391
Liver	76	79
Liver plus lung	45	47
Serosa	19	18
Brain	38	39

Table 4 Clinical characteristics of 200 metastatic solid tumor patients with CT-resistant cancer, treated with CT alone or CT plus melatonin

Characteristics	CT	CT+MLT
N	102	98
M/F	58/44	53/45
Median age (years)	61 (36–74)	60 (37–75)
Median PS (Karnofsky)	100 (90–100)	100 (90–100)
Tumor histotype		
Non-small cell lung cancer	43	41
Cisplatin/etoposide	18	16
Cisplatin/taxol	11	10
Cisplatin/gemcitabine	14	14
Colorectal cancer	26	25
5-Fluorouracil/folates	14	13
Raltitrexed	12	12
Gastric cancer		
Cisplatin/epirubicin/5-fluorouracil/folates	11	12
Soft tissue sarcomas	22	20
Adriamycin/ifosfamide	12	11
Ifosfamide	10	9
Dominant metastasis sites		
Soft tissues	6	5
Bone	14	13
Lung	44	43
Liver	21	22
Lung + liver	8	9
Serosa	4	4
Brain	5	6

(CR) or partial response (PR) was achieved in any patient treated with supportive care alone. In contrast, a PR was observed in 17 out of the 722 (2%) treated with MLT plus supportive care. This difference was statistically significant ($P < 0.05$ vs supportive care alone). Moreover, the percentage of stable disease (SD) achieved in patients concomitantly treated with MLT was significantly higher than that in patients treated with supportive care alone (171 of 722 vs 54 of 718, $P < 0.001$). Figure 1 illustrates the survival curves observed in the two groups of pa-

**Fig. 1** Percentage 1-year survival in 1,440 patients with untreatable advanced solid tumors treated with supportive care alone or supportive care plus melatonin (MLT)**Table 5** Clinical results in 1,440 patients with untreatable advanced solid tumor patients treated with supportive care alone or supportive care plus MLT (PR partial response, SD stable disease)

Tumor histotype	Clinical response (WHO)					
	Supportive care			Supportive care+MLT		
	n	PR	SD	n	PR	SD
Non-small-cell lung cancer	180	0	7 (9%)	183	3 (2%)	48 (26%)
Small cell lung cancer	12	0	0	11	0	1 (9%)
Colorectal cancer	137	0	16 (12%)	142	4 (3%)	41 (29%)
Gastric cancer	50	0	4 (8%)	48	1 (2%)	12 (25%)
Pancreatic cancer	35	0	2 (6%)	38	1 (3%)	6 (16%)
Hepatocarcinoma	17	0	3 (18%)	19	1 (5%)	6 (31%)
Biliary tract cancer	40	0	3 (8%)	36	1 (3%)	5 (14%)
Breast cancer	60	0	6 (10%)	58	1 (2%)	14 (24%)
Prostate cancer	17	0	4 (23%)	19	2 (11%)	6 (32%)
Ovarian cancer	11	0	0	9	0	1 (11%)
Cervix cancer	13	0	1 (8%)	14	0	2 (14%)
Endometrial cancer	7	0	1 (14%)	7	0	2 (14%)
Renal cell cancer	26	0	2 (8%)	28	1 (4%)	7 (25%)
Bladder cancer	6	0	0	6	0	2 (33%)
Testis cancer	7	0	0	6	0	0
Melanoma	41	0	0	37	1 (3%)	6 (16%)
Soft tissue sarcoma	21	0	3 (14%)	19	0	4 (21%)
Head and neck cancer	20	0	2 (10%)	21	0	5 (24%)
Brain glioblastoma	18	0	0	21	1 (5%)	3 (14%)
Overall tumors	718	0	54 (7%)	722	17 (2%)*	171 (24%)**

* $P < 0.05$ vs supportive care; ** $P < 0.001$ vs supportive care

Table 6 Efficacy of MLT therapy + supportive care vs supportive care alone in the treatment of cancer progression-related symptoms

Main symptoms	Supportive care (N=718)	Supportive care+MLT (N=722)
Cachexia	189 (26%)	37 (5%)*
Asthenia (n)	292 (41%)	126 (17%)*
Anorexia	226 (31%)	149 (21%)**
Depressive symptoms	164 (23%)	96 (13%)**
Anemia (Hb<10)	218 (30%)	186 (26%)*
Thrombocytopenia (platelets<100,000)	78 (11%)	21 (3%)*
Lymphocytopenia (lymphocytes<1,500)	489 (68%)	204 (28%)*

* $P<0.001$ vs supportive care;** $P<0.01$ vs supportive care**Table 7** Clinical response (WHO) in 200 patients with metastatic solid tumors treated with CT or CT plus MLT

CT regimen	CT					CT+MLT				
	n	CR	PR	CR+PR	SD	n	CR	PR	CR+PR	SD
Cisplatin/etoposide	18	0	3 (19%)	3 (19%)	5 (28%)	16	1 (6%)	4 (25%)	5 (31%)	6 (38%)
Cisplatin/taxol	11	0	4 (36%)	4 (36%)	4 (36%)	10	1 (10%)	3 (30%)	4 (40%)	4 (40%)
Cisplatin/gemcitabine	14	0	4 (29%)	4 (29%)	5 (36%)	14	0	5 (36%)	5 (36%)	5 (36%)
5-fluorouracil/folates	14	0	2 (14%)	2 (14%)	5 (36%)	13	0	3 (23%)	3 (23%)	7 (54%)
Raltitrexed	12	0	2 (17%)	2 (17%)	6 (50%)	12	0	3 (25%)	3 (25%)	7 (58%)
Cisplatin/epirubicin/5-fluorouracil/folates	11	0	3 (27%)	3 (27%)	4 (36%)	12	1 (10%)	4 (33%)	5 (42%)	5 (42%)
Adriamycin/ifosfamide	12	0	2 (17%)	2 (17%)	3 (25%)	11	0	4 (36%)	4 (36%)	5 (45%)
Ifosfamide	10	0	0	0	4 (40%)	9	0	3 (33%)	3 (33%)	4 (44%)
Overall treatments	102	0	20 (20%)	20 (20%)	36 (35%)	98	3 (3%)	29 (30%)	32 (33%)*	43 (44%)

* $P<0.05$ vs CT alone**Table 8** Main toxicities observed in 200 metastatic solid tumor patients treated with CT alone or CT plus MLT

Toxicity	CT (N=102)	CT+MLT (N=98)
Asthenia	46 (45%)	25 (26%)*
Alopecia	72 (71%)	62 (63%)
Vomiting	56 (55%)	46 (47%)
Stomatitis	36 (35%)	15 (15%)*
Diarrhea	24 (23%)	19 (19%)
Neurotoxicity	26 (25%)	8 (8%)*
Nephrotoxicity	6 (6%)	0*
Cardiotoxicity	9 (9%)	2 (2%)*
Leukopenia	18 (18%)	14 (14%)
Anemia	14 (14%)	12 (12%)
Thrombocytopenia	17 (17%)	2 (2%)*

* $P<0.05$; ** $P<0.01$; *** $P<0.001$ vs CT alone

tients. The percentage 1-year survival achieved in patients treated with MLT plus supportive care was significantly higher than that found in the supportive care only group ($P<0.005$). Table 6 shows the results obtained in prevention of the most common cancer-progression-related symptoms. Neoplastic cachexia, asthenia, anorexia, depressive symptoms, thrombocytopenia and lymphocytopenia were significantly more frequent in patients treated with supportive care alone than in those concomitantly treated with MLT ($P<0.001$, $P<0.001$, $P<0.01$, $P<0.01$, $P<0.001$, $P<0.001$, respectively). In contrast, no signifi-

cant difference was observed in the frequency of anemia. The clinical responses obtained in patients treated with chemotherapy alone and with chemotherapy plus MLT are reported in Table 7, while Table 8 shows the main toxicities found in the two groups of patients. No CR was achieved in any patient treated with chemotherapy alone, whereas CR was achieved in 3 (3%) of the 98 patients concomitantly treated with MLT. A PR occurred in 20 (20%) of the 102 patients treated with chemotherapy alone and in 29 (30%) of the 98 who also received MLT. Therefore, the percentage of objective tumor regressions (CR+PR) achieved in patients concomitantly treated with MLT was significantly higher than that observed in patients treated with chemotherapy alone ($P<0.05$). Moreover, the concomitant administration of MLT significantly reduced the percentage of patients with asthenia (25 out of 98 vs 46 out of 102, $P<0.01$), thrombocytopenia (2 of 98 vs 17/102, $P<0.001$), neurotoxicity (8 of 98 vs 26 of 102, $P<0.001$), cardiotoxicity (2 of 98 vs 9 of 102, $P<0.05$) and stomatitis (15 of 98 vs 36 of 102, $P<0.05$), whereas there was no significant difference between the groups in the percentages with alopecia, vomiting, diarrhea, leukopenia and anemia. Finally, Fig. 2 illustrates the 1-year survival curves obtained for the two groups of patients. The 1-year survival curve achieved in patients concomitantly treated with MLT was significantly higher than that for patients who received chemotherapy alone ($P<0.05$).

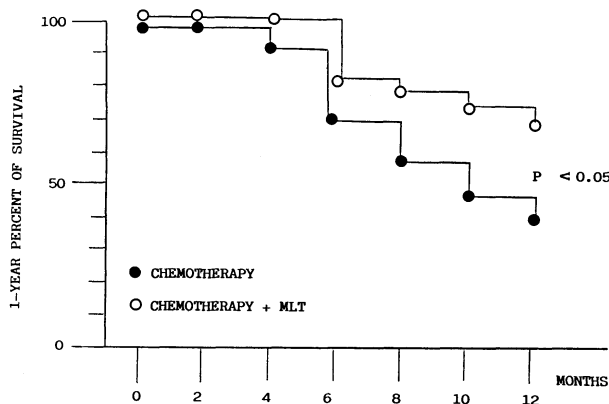


Fig. 2 Percentage 1-year survival in 200 patients with metastatic untreated solid tumors treated with chemotherapy alone or chemotherapy plus melatonin

No important MLT-related toxicity occurred. Headache and paradoxical insomnia were seen in 15 of 820 (2%) and 24 of 820 (3%) patients only. In contrast, most patients experienced an anti-anxiety effect after MLT administration.

Discussion

The results of this study, carried out in a large number of advanced cancer patients suffering from most solid tumor histotypes, clearly confirm those recorded in previous preliminary clinical investigations, showing the efficacy of the pineal hormone MLT in both curative and palliative treatment of human advanced solid malignancies. In more detail, MLT has been shown to induce disease stabilization and prolong survival in advanced cancer patients who have failed to respond to conventional anticancer therapies and for whom no other standard treatment may be available. Non-small-cell lung cancer, colorectal cancer, gastric cancer, hepatocarcinoma and prostate cancer are the neoplasms with which most benefit in terms of disease stabilization was gained from MLT therapy. Moreover, this study also confirms the results previously reported with MLT in association with chemotherapy in

cancer patients with poor clinical condition [15] in advanced cancer patients with normal clinical status. In particular, MLT has been shown to enhance both tumor response rate and survival time obtained in response to chemotherapy in cancer patients with neoplasms that are commonly less responsive to chemotherapy alone. Moreover, in addition to the previous results showing that the pineal hormone may improve the efficacy of anthracyclines, cisplatin, 5-fluorouracil, etoposide and gemcitabine [15], this study demonstrates that taxanes, raltitrexed and ifosfamide can be successfully modulated by MLT.

The therapeutic properties of MLT are not surprising, since it has been shown to be able to influence host-tumor interactions through several biological mechanisms, which may modify both tumor and host characteristics [4, 5, 6]. Moreover, in addition to its well-documented antiproliferative and immunostimulatory effects [4, 5, 6], recent studies suggest that MLT may also act as an anti-cancer molecule by exerting anti-angiogenic effects [17] and anti-inflammatory activity [14] consisting in the inhibition of IL-6 secretion, which has been proven to suppress host anticancer immunity [2, 9].

In conclusion, this study confirms that the pineal hormone MLT may have a role in the supportive care of cancer patients, since it may be effective in the prevention of both cancer progression-related symptoms, namely cachexia, asthenia and lymphocytopenia, and chemotherapy-induced toxicity, namely thrombocytopenia, asthenia, and neurocardiotoxicity. In addition, the study shows that MLT may have potential anticancer activity whether given alone or in association with cancer chemotherapy. Therefore, MLT is the first known natural molecule that may have both curative and palliative actions in the treatment of human neoplasms. A similar statement can be proposed only for progestational agents, whose efficacy, however, is generally limited to endocrine-dependent tumors, specifically breast and endometrial cancers, whereas MLT is potentially effective against most solid tumor histotypes. Finally, this study, by showing that MLT is effective in both curative and palliative treatment of human neoplasms, suggests that the artificial separation between therapeutic and supportive care in cancer has to be abrogated.

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