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Original Paper

Decreased Toxicity and Increased Efficacy of Cancer Chemotherapy Using the Pineal Hormone Melatonin in Metastatic Solid Tumour Patients with Poor Clinical Status

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Melatonin (MLT) has been proven to counteract chemotherapy toxicity, by acting as an anti-oxidant agent, and to promote apoptosis of cancer cells, so enhancing chemotherapy cytotoxicity. The aim of this study was to evaluate the effects of concomitant MLT administration on toxicity and efficacy of several chemotherapeutic combinations in advanced cancer patients with poor clinical status. The study included 250 metastatic solid tumour patients (lung cancer, 104; breast cancer, 77; gastro-intestinal tract neoplasms, 42; head and neck cancers, 27), who were randomised to receive MLT (20 mg/day orally every day) plus chemotherapy, or chemotherapy alone. Chemotherapy consisted of cisplatin (CDDP) plus etoposide or gemcitabine alone for lung cancer, doxorubicin alone, mitoxantrone alone or paclitaxel alone for breast cancer, 5-FU plus folinic acid for gastro-intestinal tumours and 5-FU plus CDDP for head and neck cancers. The 1-year survival rate and the objective tumour regression rate were significantly higher in patients concomitantly treated with MLT than in those who received chemotherapy (CT) alone (tumour response rate: 42/124 CT + MLT versus 19/126 CT only, $P < 0.001$; 1-year survival: 63/124 CT + MLT versus 29/126 CT only, $P < 0.001$). Moreover, the concomitant administration of MLT significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis and asthenia. This study indicates that the pineal hormone MLT may enhance the efficacy of chemotherapy and reduce its toxicity, at least in advanced cancer patients of poor clinical status. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: chemotherapy toxicity, melatonin, pineal gland, supportive care
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INTRODUCTION

RECENT ADVANCES in psychoneuroimmunology have improved our knowledge of biological mechanisms responsible for the toxicity of cancer chemotherapy and allowed the possibility of manipulating biological systems in an attempt to enhance resistance to chemotherapy toxicity, for example, the well demonstrated, circadian rhythm effect on chemotherapy toxicity [1, 2]. Within the neuroendocrine system, the pineal gland has been proven to play a fundamental role in the regulation of biological rhythms [3, 4], and to be involved in the control of cell differentiation and proliferation [5]. In addition, the pineal gland has been shown to exert a major role in mediating the influence of the psychoneuroendocrine system on cancer growth [3–6]. In fact, suppression of the pineal endocrine function has been suggested to induce immunosuppression and to promote cancer cell development [7].

Advanced cancer patients may often present with a pineal endocrine hypofunction, mainly consisting of a progressive decline in the physiological increase in its most investigated indole hormone, melatonin (MLT), during the dark period of the day [8–12]. Preliminary clinical studies have suggested that MLT palliative therapy may be effective in the treatment of cancer-related cachexia and fatigue in advanced cancer patients, as well as able to induce stabilisation of disease in untreatable metastatic solid neoplasms [12, 13]. In addition, MLT has been shown to have possibly direct oncostatic

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activity by several mechanisms, including control of oncogene expression, induction of cancer cell apoptosis, inhibition of free radical generation, and immunomodulating activity, mainly consisting of activation of IL-2-dependent anticancer immunity [14–17]. Moreover, since chemotherapy toxicity may depend at least in part on free radical production, MLT, which is the most active anti-oxidant natural agent currently available [18], could be effective in the treatment of chemotherapy toxicity. Preliminary studies have shown that MLT may reduce the side-effects induced by several chemotherapeutic regimens, including cardiotoxicity of anthracyclines [19], nephrotoxicity and neurotoxicity of cisplatin [20] and toxicity of 5-fluorouracil (5-FU) [21]. The aim of this study was to evaluate the influence of a concomitant MLT administration on clinical response, survival time and toxicity during the treatment of cancer patients with metastatic solid neoplasms and poor clinical status, using some of the most common therapeutic regimens.

MATERIALS AND METHODS

From January 1996 to November 1998, 250 consecutive patients with metastatic solid tumour (men 141, women 109; median age: 60 years, range 38–81 years), who were admitted to the Radiation Oncology Division of S. Gerardo Hospital of Monza, were entered into the study. Eligibility criteria were: histologically proven metastatic non-small cell lung cancer (NSCLC), breast cancer, gastro-intestinal tract tumours or head and neck cancers; measurable lesions; no brain metastases; poor clinical status because of age, low performance status (PS); heavy chemotherapeutic pretreatments or important medical illnesses other than cancer; and life expectancy of longer than 6 months. The clinical characteristics of patients are reported in Table 1.

The experimental protocol was explained to each patient, and written consent was obtained. After stratification according to tumour histotype and chemotherapy, patients were randomised to be treated with chemotherapy alone or chemotherapy plus MLT. Patients were randomised according to the tables of random numbers, and the randomisation occurred after patient acceptance to be included within the trial (Figure 1). NSCLC patients were treated with cisplatin (CDDP) plus etoposide (VP-16), or with gemcitabine (GEM) alone for patients pretreated with chemotherapeutic combinations containing CDDP. Three cycles were planned of both CDDP/VP-16 and GEM. Breast cancer patients were treated with monochemotherapy consisting of doxorubicin (DOX), mitoxantrone or paclitaxel, depending on the previous chemotherapy for each patient. DOX was injected weekly and eight cycles were planned. In addition, three cycles were planned for both mitoxantrone and paclitaxel. Patients with gastro-intestinal tract tumour received 5-FU plus folinic acid, with five cycles planned. Patients with head

Table 1. *Clinical characteristics of* 250 *metastatic solid tumour patients treated with intravenous chemotherapy (CT) alone or CT plus melatonin (MLT)*

Characteristics	CT ($n = 126$)	CT + MLT ($n = 124$)
Male	70	71
Female	56	53
Median age (range)	59 (39 – 81) years	61 (42 – 80) years
Median performance status (Karnofsky) (range)	80% (50 – 90)	80% (50 – 90)
Previous chemotherapy		
Yes	56	58
No	70	66
Histotype and chemotherapy*		
Non-small cell lung cancer	52	52
Cisplatin (CDDP) + etoposide (VP-16)	40	38
Gemcitabine (GEM)	12	14
Breast cancer	38	39
Doxorubicin (DOX)	19	21
Mitoxantrone	13	11
Paclitaxel	6	7
Gastro-intestinal tract tumours		
5-Fluorouracil (5-FU) + folinic acid (FA)	22	20
Colorectal cancer	14	11
Gastric cancer	6	6
Pancreatic cancer	2	3
Head and neck cancers		
5-FU + CDDP	14	13
Dominant metastasis sites		
Soft tissues	9	8
Bone	31	29
Lung	46	47
Liver	22	21
Lung + liver	18	19

*CDDP + VP-16: CDDP 20 mg/m^2/day + VP-16 100 mg/m^2/day, days 1–3, every 28 days. GEM: 1000 mg/m^2 days 1, 8 and 15, every 28 days. DOX: 20 mg/m^2/weekly. Mitoxantrone 14 mg/m^2, every 21 days. Paclitaxel 175 mg/m^2, every 28 days. 5-FU + FA: 5-FU 375/mg/m^2/day + FA 10 mg/m^2/day, days 1–5, every 28 days. 5-FU + CDDP: 5-FU 200 mg/m^2/day + CDDP 20 mg/m^2/day, days 1–5, every 28 days.

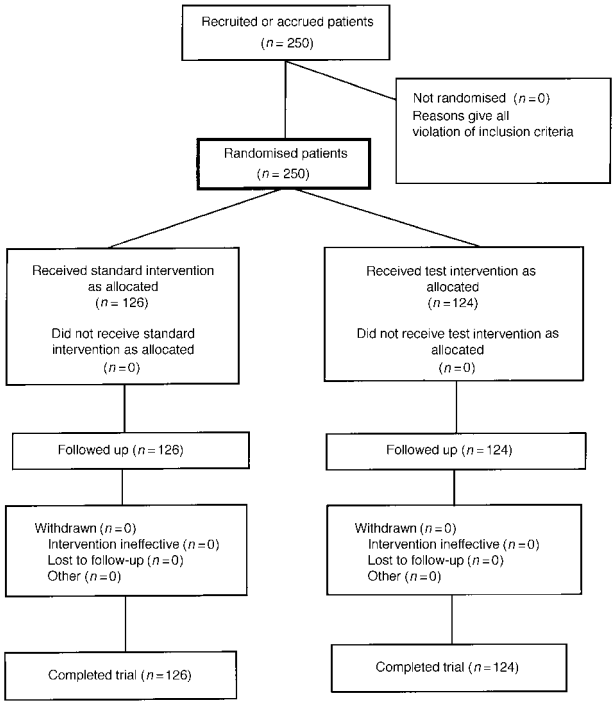

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639).

and neck cancers were treated with CDDP plus 5-FU for three cycles. The dosage and schedule of chemotherapies are reported in Table 1. All chemotherapeutic protocols were administered at the same time, and the previous chemotherapies were substituted at the time of cancer progression on treatment. The new chemotherapy was injected after an interval of at least 1 month after the progression of the previous chemotherapy. MLT was supplied by Helsinn-Chemicals (Breganzona, Switzerland). According to previous experimental and clinical studies [9–17], MLT was given orally at a dose of 20 mg/day in the evening, every day, starting 7 days prior to chemotherapy as an induction phase. MLT administration was continued after chemotherapy interruption, until disease progression.

Clinical response and toxicity were evaluated according to World Health Organization (WHO) criteria, by planning radiological examinations before the onset of treatment, and at 2 monthly intervals. Complete response (CR) was defined as the complete regression of all neoplastic lesions for at least 1 month. Partial response (PR) was defined as a reduction greater than 50% of the sum of the two longest perpendicular diameters of all lesions for at least 1 month. Stable disease (SD was defined as no increase or decrease greater than 25% of the neoplastic lesions. Finally, progressive disease (PD) was defined as an increase greater than 25% of the neoplastic lesions or the appearance of new lesions. Data were statistically analysed by the chi-square test or Student's *t*-test, as appropriate. Age distribution was evaluated by the zed-distribution method. Median and minimum follow-up were 26 (range 36–12) months and 12 months, respectively. The number of patients needed was calculated so as to be able to demonstrate a possible increase in the percentage of 1-year survival greater than 30% with respect to that expected according to results observed in a historical control group treated with chemotherapy alone. Alpha and beta errors were 5 and 10%, respectively, and the potency of test was 90%. 1-year survival curves were plotted according to the Kaplan–Meier method, and statistically analysed by the log-rank test.

RESULTS

As reported in Table 1, the two groups of patients treated with or without MLT were well balanced for the main prognostic variables, including tumour histotype, dominant metastasis sites, previous chemotherapy, age distribution and PS. The clinical response of the two groups is reported in Table 2. No patient (0/126) treated with chemotherapy alone achieved a CR, whilst a CR was obtained in 6/124 (5%) patients treated with chemotherapy plus MLT ($P<0.02$; NSCLC, 2; breast cancer, 2; gastro-intestinal tumours, 1; head and neck cancer, 1). A PR was obtained in 36/124 (29%) patients concomitantly treated with MLT and in only 19/126 (15%) patients treated with chemotherapy alone ($P<0.01$). The objective tumour regression rate (CR + PR) was significantly higher in the MLT group than in patients who received chemotherapy alone (42/124 versus 19/126, $P<0.001$). The regression rate tended to be higher in patients concomitantly treated with MLT also in relation to the different chemotherapeutic regimens, except for mitoxantrone, although statistical significance was reached only for CDDP plus VP-16 in NSCLC ($P<0.001$), 5-FU plus folinic acid in gastro-intestinal tract tumours ($P<0.05$) and DOX for breast cancer ($P<0.05$). The median time to progression was 9 months (range 4–14 months) for the MLT group and 4 months (range 3–6 months) for patients treated with

Table 2. Clinical response in 250 *metastatic solid tumour patients treated with chemotherapy (CT) alone or CT plus melatonin (MLT)*

	Clinical response											
	CT						CT + MLT					
Chemotherapeutic regimen	*n*	CR	PR	CR + PR (%)	SD	PD	*n*	CR	PR	CR + PR (%)	SD	PD
Cisplatin + VP-16	40	0	7	7 (18)	18	15	38	2	12	14 (37)*	16	8
Gemcitabine	12	0	1	1 (8)	7	4	14	0	4	4 (29)	7	3
Doxorubicin	19	0	6	6 (32)	6	7	21	1	9	10 (48)†	8	3
Mitoxantrone	13	0	1	1 (8)	5	7	11	0	1	1 (9)	6	4
Paclitaxel	6	0	0	0	3	3	7	1	1	2 (29)	4	1
5-Fluorouracil + folinic acid	22	0	2	2 (9)	8	12	20	1	5	6 (30)†	9	5
5-Fluorouracil + cisplatin	14	0	2	2 (14)	6	6	13	1	4	5 (38)	6	2
Overall treatments	126	0	19 (15%)	19 (15)	53 (42%)	54 (43%)	124	6 (5%)	36 (29%)	42 (34)*	56 (45%)	26 (21%)

*$P<0.001$ versus CT; †$P<0.05$ versus CT. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Per cent of 1-year survival in 250 metastatic solid tumour patients treated with chemotherapy (CT) alone or CT plus melatonin (MLT)

Chemotherapeutic regimen	Per cent of 1-year survival (%)	
	CT (%)	CT + MLT (%)
Cisplatin + VP 16	8/40 (20)	17/38 (45)*
Gemcitabine	2/12 (17)	6/14 (43)‡
Doxorubicin	7/19 (37)	13/21 (62)‡
Mitoxantrone	2/13 (15)	2/11 (18)
Paclitaxel	1/6 (17)	5/7 (71)‡
5-Fluorouracil + folinic acid	7/22 (32)	12/20 (60)‡
5-Fluorouracil + cisplatin	2/14 (14)	8/13 (62)†
Overall treatments	29/126 (23)	63/124 (51)*

*$P<0.001$ versus CT; †$P<0.02$ versus CT; ‡$P<0.05$ versus CT.

chemotherapy alone. Moreover, mean time to progression was significantly longer in patients concomitantly treated with MLT than in those treated with chemotherapy alone (8.9 ± 1.3 versus 4.2 ± 0.8 months, ± standard error of the mean, $P<0.05$).

One-year survival was significantly higher in patients concomitantly treated with MLT than in those who received chemotherapy alone (Table 3, $P<0.001$). The difference was statistically significant also in relation to most chemotherapeutic regimens administered, including CDDP + VP-16 ($P<0.001$), 5-FU + folinic acid ($P<0.05$), 5-FU + CDDP ($P<0.02$), GEM ($P<0.05$), DOX ($P<0.05$) and paclitaxel ($P<0.05$). Only for mitoxantrone therapy, was 1-year survival not significantly influenced by MLT. The 1-year survival curves observed in the two groups of patients are illustrated in Figure 2. The overall survival time obtained in patients concomitantly treated with MLT was significantly longer than that observed in patients who received chemotherapy alone ($P<0.05$).

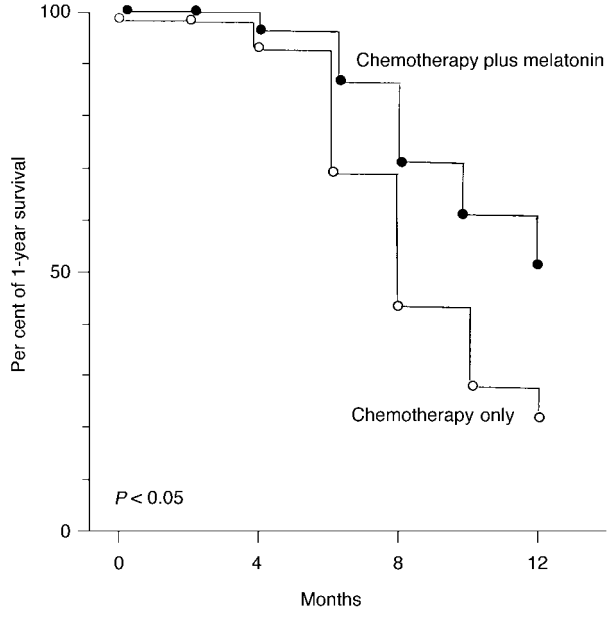

Figure 2. One-year survival curves observed in metastatic solid tumour patients of poor clinical status treated with chemotherapy plus melatonin or with chemotherapy alone.

Table 4. Main toxicities observed in 250 metastatic solid tumour patients treated with chemotherapy (CT) alone or CT plus melatonin (MLT)

Toxicity	CT ($n=126$) (%)	CT + MLT ($n=124$) (%)
Myelosuppression	54 (43)	25 (20)*
Leucopenia	22 (17)	13 (10)
Anaemia	11 (9)	8 (6)
Thrombocytopenia	31 (25)	4 (3)†
Neurotoxicity	17 (13)	3 (2)†
Nephrotoxicity	4 (3)	0
Cardiotoxicity	12 (10)	2 (2)†
Stomatitis	38 (30)	12 (10)†
Alopecia	74 (59)	63 (51)
Nausea/vomiting	72 (57)	61 (49)
Diarrhoea	24 (19)	16 (13)
Asthaenia	79 (63)	33 (27)*

*$P<0.001$ versus CT; †$P<0.05$ versus CT.

As far as the toxicity of treatments is concerned, no MLT-related toxicity occurred. Chemotherapy-induced toxicity was less pronounced in the MLT group (Table 4). The concomitant administration of MLT significantly reduced the frequency of myelosuppression ($P<0.001$), thrombocytopenia ($P<0.05$), neurotoxicity ($P<0.05$), cardiotoxicity ($P<0.05$), stomatitis ($P<0.05$) and asthenia ($P<0.001$). Leucopenia and anaemia were also less frequent in the MLT group, but did not reach statistical significance. Nausea and vomiting, diarrhoea and particularly alopecia were not influenced by MLT.

DISCUSSION

In agreement with experimental observations [19–24] and with our previous preliminary clinical data [25], this study shows that concomitant administration of the MLT, which has been proven to have very potent antioxidant, immunomodulating and oncostatic activities [19–24], reduced the toxicity and enhanced the efficacy of cancer chemotherapy in terms of both objective tumour regression and survival time. The protective action of MLT against chemotherapy toxicity is mainly the result of its capacity to act as a free radical scavenger [4, 16, 18]. In addition to this, the protection against some particular toxicities could depend on other more specific mechanisms. In particular, the protection against thrombocytopenia could be due to the well documented thrombopoietic property of MLT [22, 23], whilst the protection against neurotoxicity would depend on the neurotrophic activity of MLT and on its capacity to prevent apoptosis of neuronal cells in response to several types of damage, including viruses and chemical neurotoxic agents [26].

The increased 1-year survival rate observed in patients concomitantly treated with MLT may be explained by the ability of the pineal hormone to prevent chemotherapy-induced immunosuppression [24]. Alternatively, the increased tumour regression rate achieved in patients concomitantly treated with MLT could be due to the high antioxidant activity of the pineal hormone [16, 18, 27], which may enhance the cytotoxic potency of cancer chemotherapy, as observed in experimental conditions [27].

The optimal therapeutic strategy to be recommended for cancer patients with very advanced disease, poor clinical

status and tumour histotype less responsive to chemotherapy alone, is often discussed and chemotherapy, biotherapy with immunomodulating agents or supportive care alone are the usual choices. This study, by showing that the concomitant administration of the immunomodulating and oncostatic natural agent MLT may improve clinical efficacy and tolerability of cancer chemotherapies, would suggest that the best therapy consists of biochemotherapeutic strategies capable of controlling cancer growth without inducing a concomitant suppression of host anticancer immune defences. The natural endocrine agent MLT in association with chemotherapy could represent the 'prototype'. However, these data have been obtained in cancer patients with very advanced disease and poor clinical status, who most likely may be characterised by an endogenous deficiency of MLT itself [4, 7, 8]. Therefore, in this case, the exogenous administration of MLT could simply represent a pineal endocrine replacement therapy. Further studies with chemotherapy plus MLT in cancer patients with less extensive disease and normal clinical status will be required to establish whether the concomitant administration of MLT may enhance the efficacy of chemotherapy in routine practice. In addition, further studies, evaluating the 24-h MLT circadian rhythm preceding MLT substitution, will be required to establish whether the efficacy of MLT is related to a lack of the physiological pineal circadian rhythm or whether it is independent of the pineal endocrine status.

Our previous studies have already shown that MLT may also be successfully associated with low-dose IL-2 in the treatment of several metastatic solid neoplasms other than those which may respond to IL-2 alone, such as renal cell cancer and melanoma. Therefore, successive studies will be needed to establish whether the best results with MLT may be achieved in association with cytokines or chemotherapy.

In conclusion, this study confirms in humans the possibility of biologically manipulating toxicity and efficacy of cancer chemotherapy by the pineal hormone MLT, in patients with advanced cancer and poor clinical status. Further studies will be required to define the prognostic impact of MLT therapy on the efficacy of the single chemotherapeutic combinations in relation to the different tumour histotypes, as well as to define the influence of MLT on other commonly used chemotherapeutic agents, namely cyclophosphamide, methotrexate, ifosfamide, bleomycin, mitomycin, nitrosoureas and vinca alkaloids.

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