
Palliative oncology update

The therapeutic application of melatonin in supportive care and palliative medicine

Fade Mahmoud, MD
Nabeel Sarhill, MD
Miroslaw A. Mazurczak, MD

Abstract

Melatonin is a hormone produced mainly in the pineal gland. Plasma levels exhibit a circadian variation with the highest concentration occurring at night. The human biologic effects of melatonin depend upon the time of day it is made available. One of these effects is the setting and resetting of circadian clocks (chronobiotic effect). Additionally, it may be a potent antioxidant and immunomodulator and has been shown to have anti-tumor, anticytokine, anti-insomnia, and anticachexia effects. Melatonin

has also been shown to improve survival and performance status in patients with advanced cancer. Objective tumor response occurs with melatonin alone or when combined with interleukin-2 (IL-2). Further, melatonin reduces radiation- and chemotherapeutic-induced toxicity. Symptomatic and circadian disruption is linked to increased cancer risk. The chronobiotic capacity of melatonin to reset circadian clocks may provide a verifiable strategy to reduce cancer risk and enhance quality of life by diminishing cancer-induced circadian disruption.

Key words: melatonin, cancer, insomnia, immunotherapy, cachexia, circadian, chronobiotic

Introduction

Melatonin (N-acetyl-5 methoxytryptamine) is produced mainly in the pineal gland from the amino acid tryptophan. Other sites of production

include the retina,¹ lacrimal gland,² bone marrow,³ and the gut.⁴ Its synthesis exhibits a circadian rhythm with the highest production always occurring at night.⁵ Light transduced through light receptors within the retina passes through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and on to the pineal gland.⁶ The electrochemical activity caused by light results in the shutdown of melatonin synthesis and release within and from the pineal gland.⁷ At physiologic circulating levels, melatonin inhibits cancer cell division. At therapeutic levels, it is cytotoxic to cancer cells. At physiological and pharmacological concentrations, melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status.⁸

Melatonin has not been approved by the US Food and Drug Administration (FDA) but is available over-the-counter. Because it is unregulated,

Fade Mahmoud, MD, Department of Internal Medicine, University of South Dakota, Sioux Falls, South Dakota.

Nabeel Sarhill, MD, Hematology and Oncology, University of Texas Health Science Center, San Antonio, Texas.

Miroslaw A. Mazurczak, MD, Hematology and Oncology, University of South Dakota, Sioux Falls, South Dakota.

debate is ongoing as to its purity, safety, and efficacy. Millions of Americans use it as a sleep aid. Despite claims in magazines and newspapers, the therapeutic effects of melatonin in cancer treatment and prevention were not well-documented until quite recently.

The authors reviewed the literature regarding melatonin via a Medline search for the years 1990 to 2004 using the key words cancer, melatonin, insomnia, immunotherapy, cachexia, and chronobiotic. This article discusses the clinical benefits of melatonin as supported by the literature and why its use in palliative medicine and supportive oncology should not be overlooked.

Pharmacokinetics

Melatonin is rapidly absorbed when given orally and reaches peak plasma levels in two hours with a half-life of 30 to 60 minutes. Blood levels are normally high at night and low during the day (the so-called "hormone of darkness"). Fifty to 75 percent of melatonin is reversibly bound to plasma proteins (e.g., alpha1-acid glycoprotein, albumin).⁹ Saliva levels (70 percent lower than plasma levels) seem to reflect unbound melatonin.¹⁰ Melatonin is lipid-soluble and able to enter almost every cell in the body.¹¹

Melatonin is metabolized by liver microsomes to 6-hydroxymelatonin, which further conjugates with sulfate or glucuronide before it is excreted in the urine.¹² Melatonin plasma measurements are difficult to interpret given its circadian secretion; however, urinary excretion of 6-sulphatoxymelatonin is helpful in studying pineal function.¹⁰ Oral doses of 5 mg produce blood levels 25 times higher than normal but do not alter endogenous melatonin production.¹³ Melatonin receptors have recently been cloned (MEL1a, MEL1b, and MEL1c), the first two of which are found in humans.¹⁴

The circadian clock

To fully understand the therapeutic effects of melatonin, one should know its chronobiotic characteristics. The circadian clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. It is the primary source of the circadian rhythm.¹⁵ Melatonin is a chronobiotic that acts as a chemical messenger of the circadian clock. High-affinity G protein-coupled melatonin receptors (MEL1a receptors) are located in the suprachiasmatic nucleus of human brains.¹⁶ A second type of melatonin receptor (MEL1b receptors) is found in the retina.¹ A group of circadian-clock control genes have recently been discovered and cloned. These genes organize and set the time of normal cell and cancer cell proliferation in a circadian manner. Mutations in such genes result in spontaneous development of cancer.

It is hypothesized that decreased serum melatonin levels and/or circadian melatonin disruption may increase cancer risk. Patients with prostate cancer are found to have near absence of the usual melatonin peak.¹⁷ Further, exposure to light at night suppresses the physiologic production of melatonin and thus its antiproliferative effect on intestinal cancers. It has been shown that night-shift female workers have an increased risk of breast cancer.¹⁸ Another prospective study examined the relationship between rotating night shifts and the risk of colorectal cancer in 78,586 female nurses and found 602 cases of colorectal cancer among participants. It was concluded that working a rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer in women.¹⁹

Pharmacologic manipulation of the circadian clock and management of circadian rhythm disorders is promising. There is evidence that, by resetting the circadian clock, melatonin

therapy provides important clinical applications.¹¹ Knowledge of the human circadian rhythm aids in the administration of anticancer therapy at times when cancer cell proliferation is expected to be high.

Melatonin as a chronobiotic

A chronobiotic is a chemical capable of therapeutically reorganizing the circadian rhythm or prophylactically preventing its disruption following illness.^{11,20} Melatonin acts as a powerful chronobiotic. Exogenous administration at an appropriate circadian stage reproducibly shifts the endogenous melatonin circadian rhythm in humans.¹¹ Imagine melatonin as the factory manager and the circadian clock as the time schedule. The manager's office is located in the pineal gland of the human brain. This manager sets up, organizes, and synchronizes the time schedule for employees (different internal physiologic and pathologic functions). Cell division and apoptosis, immune functions, and all other biological events are timed within the circadian clock by melatonin, the manager.

Chronotherapy

Selecting the proper time to treat an illness is known as chronotherapy or circadian rhythm organization. Well-designed randomized clinical trials support the clinical utility of properly timed therapy. Cancer cell proliferation and DNA synthesis peak at certain points during the day. Delivering therapy at these times is a common sense. Unfortunately, anticancer therapies are scheduled according to patients' and physicians' convenience rather than for maximum efficacy. In one study, women with advanced ovarian cancer were randomized to receive a standard chemotherapy (doxorubicin hydrochloride with cisplatin) at different times during the

day. The five-year survival rate was 44 percent in those who received treatment on an optimal timing schedule (doxorubicin hydrochloride at 6 AM and cisplatin at 6 PM) versus 11 percent in those who received a suboptimal schedule (doxorubicin hydrochloride at 6 PM and cisplatin at 6 AM).

Circadian therapy also allows the use of higher doses of each agent with a decreased toxicity profile.^{11,21} Children in remission from acute lymphoblastic leukemia who received 6-mercaptopurine in the evening were three times less likely to relapse than those who took it in the morning.²² In another study, three-drug fluoropyrimidine-based chronotherapy for colorectal cancer markedly reduced all drug toxicities and doubled objective cancer response frequency.²³ Despite this evidence, few physicians incorporate chronotherapy in their clinical practice. Aaron Lerner, who discovered melatonin in 1958,²⁴ was the first to report increased sleepiness hours after melatonin intake, demonstrating its time-dependent nature.

Melatonin and cancer treatment

Antitumor effects

Melatonin is effective in stemming cancer progression and improving survival in patients with advanced cancer who have failed standard first-line therapies (Tables 1 and 2). It prevents neoplastic growth²⁵ by inhibiting cell proliferation, increasing the number of cells in apoptosis, inhibiting metastatic spread,^{8,26} and decreasing production of tumor growth factors such as prolactin and insulin-like growth factor-1.²⁷ Melatonin shows antiangiogenic activity by lowering vascular endothelial growth factor—the most active angiogenic factor.²⁸

Melatonin also significantly inhibits the growth of human uveal melanoma cells²⁹ and breast cancer cells.³⁰ Further, the growth-inhibitory

effect of tamoxifen on breast cancer cells is enhanced with melatonin.³¹ The anticancer effects of melatonin have been observed in cultured cells of ovarian carcinoma,³² human neuroblastoma,³³ pituitary tumor,³⁴ and larynx carcinoma.³⁵

Melatonin is effective in cancer immunosuppressive therapy. Interleukin-2 and melatonin combination immunosuppressive therapy results in an increase in objective tumor response and a decrease in drug toxicity.^{6,7,36-39} It is speculated that melatonin augments the antitumor activity of IL-2 by inhibiting tumor growth factor production. Objective tumor response was reported in 27 percent of patients with kidney cancer who received both melatonin and interferon compared with 10 to 15 percent for those receiving interferon alone.³⁹ Further, low-dose interleukin-2 and cisplatin combined with melatonin was found to be an effective and well-tolerated second line therapy for metastatic melanoma with an outcome at least comparable to dacarbazine plus interferon-alpha.⁴⁰ Melatonin and tamoxifen have been used as single agents in the palliative treatment of metastatic tumors without clear efficacy.²⁷ However, melatonin and tamoxifen combination therapy was shown to control cancer progression and improved performance status in patients with advanced cancer.²⁷

Palliation of side effects

Melatonin protects healthy cells from radiation- and chemotherapy-induced toxicity.^{41,42} It has been shown to protect the skin from ultraviolet oxidative damage⁴³ and to activate the enzymes involved in the repair of cellular DNA lesions after radiation therapy. Moreover, melatonin inhibits the production of free radicals, which play a part in mediating the toxicity of chemotherapy.⁴²

Melatonin as a prognostic or diagnostic marker

Patients with positive estrogen and/or progesterone receptors of primary breast cancer have lower nocturnal melatonin levels than age-matched healthy controls.^{44,45} The degree of receptor positivity correlates with the degree of melatonin reduction in the breast tissue. Moreover, melatonin levels in tumor tissue inversely correlate with tumor size in primary breast cancer.⁴⁶ Hence, decreased melatonin levels in breast cancer may indicate a poor prognosis. The negative correlation between melatonin tissue levels and the tumor proliferative index is reported in lung, prostate, and gastrointestinal tumors.^{46,47} Patients with choroidal melanomas have higher levels of serum melatonin compared with healthy controls. After surgical correction (either enucleation or transpupillary thermotherapy), a constant decrease of serum melatonin has been documented ($P < 0.003$).⁴⁸ The use of melatonin as a marker for diagnosis or prognosis warrants additional investigation.⁴⁹

Melatonin and cachexia

It is speculated that melatonin counteracts cancer cachexia and improves quality of life (QOL) in patients with advanced cancer (Table 3).^{50,51} Melatonin modifies many cytokines including tumor necrosis factor,^{42,52} interleukins 1, 2, and 6, and gamma-interferon.^{53,54} One study found a significant decrease in interleukin-6 circulating levels 30 days following a 10 mg daily oral dose of melatonin in 31 patients with advanced cancer.⁵⁵ The relationship between melatonin and tumor necrosis factor was investigated in 100 patients with advanced cancer receiving either supportive care alone or supportive care plus melatonin (20 mg/d each night) for at least two

Table 1. Randomized controlled trials of melatonin in the treatment of advanced cancer

Reference	N	Diagnosis	Therapy	Results and conclusions
Lissoni et al. ⁵¹	30	melanoma	no treatment or po melatonin 20 mg/d	Disease-free survival higher in melatonin-treated patients; no melatonin-related toxicity; melatonin may be effective in preventing disease progression in node-relapsed melanoma patients.
Lissoni et al. ⁵⁷	63	non-small cell lung cancer	po melatonin 10 mg/d (n = 31) or supportive care only (n = 32)	Stable disease and 1-year survival higher in melatonin group (p < 0.05); no melatonin-related toxicity; performance status better with melatonin; melatonin prolonged survival in metastatic non-small cell lung cancer that failed cisplatin chemotherapy.
Lissoni et al. ⁵⁹	70	non-small cell lung cancer	chemotherapy alone (n = 36) or chemotherapy + po melatonin 20 mg/d (n = 34)	Complete response in 1/34 patients concomitantly treated with melatonin, 0 in the chemotherapy group alone; partial response in 10 and in 6 patients treated with or without melatonin, respectively; tumor response rate higher in patients receiving melatonin (11/34 vs. 6/35); survival significantly higher in patients treated with melatonin + chemotherapy than in those who received chemotherapy alone (15/34 vs. 7/36, p < 0.05); chemotherapy well-tolerated in the melatonin group; myelosuppression, neuropathy, and cachexia significantly lower in the melatonin group; concomitant administration of melatonin may improve the efficacy of chemotherapy (mainly in terms of survival time) and reduced chemotherapy toxicity.
Lissoni et al. ¹⁰³	80	advanced solid tumors	subcutaneous IL-2 (3 million IU/d) + po melatonin 40 mg/d (n = 41) or subcutaneous IL-2 (3 million IU/d) (n = 39)	Complete response in 3 patients, partial response in 8 patients with IL-2 + melatonin; complete response in 0 patients, partial response in 1 patient with IL-2 alone; 1-year survival significantly higher in IL-2 + melatonin group than with IL-2 alone (19/41 vs. 6/39, p < 0.05); melatonin may increase the efficacy of subcutaneous IL-2 therapy.
Lissoni et al. ¹⁰⁴	50	metastatic colorectal cancer	subcutaneous IL-2 (3 million IU/d) + po melatonin 40 mg/d (n = 25) or supportive care (n = 25)	Partial response in 3 patients on melatonin + IL-2; no response in patients receiving supportive care alone; survival was higher in the immunotherapy than the supportive-care group (9/25 vs. 3/25, p < 0.05); IL-2 + melatonin may be effective as a second-line therapy in metastatic colorectal cancer progressed under 5-fluorouracil and folate.
Lissoni et al. ¹⁰⁵	250	lung (104), breast (77), GI (42), head and neck (27)	po melatonin 20 mg/d + chemotherapy (n = 124) or chemotherapy alone (n = 126)	Survival and tumor response significantly better in melatonin compared with chemotherapy (tumor response in 42/124 patients with chemotherapy + melatonin vs. 19/126 for chemotherapy alone); 1-year survival 63/124 with chemotherapy + melatonin versus 29/126 for chemotherapy alone (p < 0.001); melatonin significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis, and asthenia (p < 0.05).
Lissoni et al. ¹⁰⁶	50	brain metastasis	supportive care or supportive care + po melatonin 20 mg/d	Survival significantly higher in the melatonin + supportive-care group than in the supportive-care group alone; melatonin may improve survival and QOL in patients with brain metastases.
Lissoni et al. ¹⁰⁷	30	glioblastoma	radiation therapy alone (60 Gy) or radiation therapy + po melatonin 20 mg/d	Survival significantly higher with radiation therapy + melatonin than with radiation therapy alone (6/14 vs. 1/16, p < 0.02); radiation therapy-related toxicity lower in those concomitantly treated with melatonin (p < 0.025); melatonin may prolong survival time and improve QOL in patients affected by glioblastoma.

Table 1. Randomized controlled trials of melatonin in the treatment of advanced cancer (continued)

Reference	N	Diagnosis	Therapy	Results and conclusions
Barni et al. ¹⁰⁸	40	melanoma	melatonin 5 mg/m ² /d to 700 mg/m ² /d in four divided doses	Six patients had partial response and 6 had stable disease at median of five weeks; median response duration was 33 weeks; side effects were minimal with fatigue being the most common (17/40 patients).
Aldeghi et al. ¹⁰⁹	100	solid tumors	subcutaneous IL-2 (3 million IU/d) + po melatonin 40 mg/d (n = 52) or supportive care alone (n = 48)	Tumor regression seen in 9 patients treated with immunotherapy and in none treated with supportive care alone; survival significantly higher in the immunotherapy group than in the supportive-care group (21/52 vs. 5/48, p < 0.005); performance status improved in 22 patients in the immunotherapy group and in 8 patients in the supportive-care group (p < 0.01); cancer neuroimmunotherapy with low-dose IL-2 and melatonin may prolong survival and improve QOL in patients with metastatic solid tumors who failed conventional therapies.
Lissoni et al. ⁴⁰	73	solid tumors	po melatonin alone 20 mg/d (n = 37) or melatonin + po 5-MTT 1 mg/d (n = 36)	Partial response in 2 patients treated with melatonin + 5-MTT and in 0 patients receiving melatonin alone; stable disease in 2 patients receiving melatonin alone and in 8 patients receiving melatonin + 5-MTT; the less-known pineal indole 5-MTT also has antiproliferative and immunomodulating effects and may further amplify the oncostatic activity of melatonin in advanced untreatable human solid neoplasms.
Lissoni et al. ¹¹¹	30	renal cell carcinoma	IL-2 + po morphine 60-120 mg/d (n = 16) or IL-2 + po morphine + melatonin (n = 14)	Partial response significantly higher in the melatonin group (4/14 vs. 1/16, p < 0.05); 3-year survival significantly higher in the melatonin group (p < 0.01); melatonin didn't affect morphine analgesia; melatonin may abrogate opioid-induced immunosuppression.
Cerea et al. ¹¹²	30	colorectal	irinotecan alone (125 mg/m ² /week IV for 9 consecutive weeks) (n = 16) or irinotecan + melatonin (20 mg po daily at night) (n = 14)	Complete response 0; partial response in 2/16 patients treated with irinotecan alone and in 5/14 patients treated with irinotecan + melatonin; stable disease in 5/16 patients treated with irinotecan alone and in 7/14 patients treated with irinotecan + melatonin; 4 percent disease control in patients concomitantly treated with melatonin was significantly higher than that observed in those treated with chemotherapy alone (12/14 vs. 7/16, p < 0.05).

5-MTT: 5-methoxytryptamine; IL-2: interleukin-2.

months. Patients on supportive care and melatonin were found to have significantly less weight loss (3 kg vs. 16 kg) and less disease progression (53 percent vs. 90 percent) than those on supportive care alone. Mean serum tumor necrosis factor levels were also significantly lower.³⁶ Proinflammatory cytokines, such as tumor necrosis factor and interleukin-6, have been strongly implicated in the etiology of

cancer-related cachexia. Melatonin, by inhibiting those cytokines, may play a role in anticachexia.

Melatonin and survival

Melatonin prolongs survival in patients with melanoma⁵⁶ and lung cancer⁵⁷ (Tables 1 and 2). Another study found that melatonin given orally (20 mg/d) at 8 PM was associated

with a greater one-year survival rate in patients with brain metastases than in those receiving supportive care alone.⁵⁸ Moreover, patients receiving both melatonin and radiation for untreatable glioblastoma had an increased one-year survival rate and a concomitant reduction in radiation-induced toxicity compared with those receiving radiotherapy alone.⁵⁹ Melatonin immunotherapy combined

Table 2. Uncontrolled clinical trials of melatonin in the treatment of advanced cancer				
Reference	N	Diagnosis	Therapy	Conclusion
Lissoni et al. ⁷¹	14	lung (4), gastric (3), mesothelioma (2), hepatic (2), pancreatic (1), melanoma (1), colon (1)	subcutaneous IL-2 (3 million IU/d) + melatonin 40 mg/d + 5-MTT 1 mg/d	Partial response in 4 patients (lung 2, hepatic 1, mesothelioma, 1); stable disease in 6, progressive disease in 4; neuroimmunotherapy with IL-2 + melatonin and 5-MTT is a well-tolerated and potentially effective therapy in advanced solid tumors.
Lissoni et al. ²⁸	20	various cancer types	po melatonin 20 mg/d for at least 2 months	Partial response in 2 patients, stable disease in 6, progressive disease in 12; VEGF mean levels decreased on therapy and showed a significant decline in nonprogressing patients but not in progressing patients; melatonin is associated with reduced VEGF secretion, suggesting that it may control tumor growth in part by acting as a natural antiangiogenic.
Lissoni et al. ³⁶	14	lung (6), kidney (4), stomach (2), liver (1), melanoma (1)	subcutaneous IL-2 (3 million IU/d) + po melatonin 40 mg/d	Partial response in 3 patients, stable disease in 6, progressive disease in 5; partial response and stable disease were associated with significantly longer survival and/or increase in mean lymphocytes and eosinophils; melatonin acts by inducing IL-2 antitumor immune effect and/or by increasing cancer cell cytotoxicity mediated by IL-2-induced cytotoxic lymphocytes.
Lissoni et al. ³⁸	14	advanced endocrine	subcutaneous IL-2 (3 million IU/d) + po melatonin 40 mg/d	Partial response in 3 patients (carcinoid 1, neuroendocrine lung tumor 1, pancreatic islet cell tumor 1)
Lissoni et al. ⁴¹	80	lung (35), breast (31), GI (14)	chemotherapy + po melatonin 20 mg/d or chemotherapy alone	Malaise, asthenia, thrombocytopenia, and neuropathy significantly less frequent in patients receiving melatonin; alopecia and vomiting were not influenced by melatonin; melatonin may prevent some chemotherapy-induced side effects.
Lissoni et al. ⁷²	14	breast	po melatonin 20 mg/d + po tamoxifen 20 mg/d	Partial response in 4/14 patients (median duration 8 months); treatment was well-tolerated. Mean serum levels of IGF-1 significantly decreased with therapy ($p < 0.01$); concomitant therapy with melatonin may induce objective tumor response in advanced breast cancer patients refractory to tamoxifen alone.
Lissoni et al. ¹⁰¹	25	unknown primary (6), melanoma (4), cervical (4), pancreatic (5), hepatic (3), ovarian (2), non-small cell lung cancer (1)	po tamoxifen 20 mg/d + melatonin 20 mg/d	Partial response in 3 patients (cervix 1, melanoma 1, unknown primary 1); 13 had stable disease and 9 had progressive disease; performance status improved in 9 patients; 7 patients survived >1 year.
Lissoni et al. ¹¹³	35	colon (14), gastric (8), hepatic (6), pancreatic (7)	po melatonin 50 mg/d + subcutaneous IL-2 (3 million IU/d)	Complete response in 2 patients (gastric 1, hepatic 1), partial response in 6 (gastric 2, hepatic 2, colon 1, pancreas 1); stable disease occurred in 11/35 and progressive disease in 16/35 patients; IL-2 + melatonin is safe and effective in advanced GI tumors.
Lissoni et al. ¹¹⁴	54	lung, pancreatic, or colon	melatonin 20 mg at night	Partial response in 3 patients (pancreas, colon, and hepatic), stable disease in 21, progressive disease in 30; performance status improved in 18 patients (33 percent); tumor response and QOL improved in some cancer patients for whom no other standard therapy was available.

Table 2. Uncontrolled clinical trials of melatonin in the treatment of advanced cancer (continued)

Reference	N	Diagnosis	Therapy	Conclusion
Lissoni et al. ¹¹⁵	14	gastric	subcutaneous IL-2 (3 million IU/d) + po melatonin 50 mg/d	Complete response in 1 patient, partial response in 2, stable disease in 6, progressive disease in 5; toxicity low in all cases; combination of IL-2 and melatonin may represent a new well-tolerated biotherapy capable of inducing objective tumor regression in patients with metastatic gastric cancer and low performance status.
Lissoni et al. ¹¹⁶	12	non-Hodgkin's lymphoma (6), Hodgkin's disease (2), multiple myeloma (2), acute myeloblastic leukemia (1), chronic monomyelocytic leukemia (1)	subcutaneous IL-2 (3 million IU/d) + po melatonin 20 mg/d	Partial response in 1 patient (multiple myeloma), stable disease in 7 (non-Hodgkin's lymphoma 3, Hodgkin's disease 1, acute myeloblastic leukemia 1, chronic monomyelocytic leukemia 1, multiple myeloma 1), and progressive disease in 4; partial response or stable disease was maintained for a median duration of 21 months.
Barni et al. ¹¹⁷	14	colon	IM melatonin 20 mg/d	Partial response in 1 patient, stable disease in 3, and progressive disease in 10; performance status improved in 5 patients; melatonin did not have significant antitumor activity in metastatic colorectal cancer patients resistant to fluorouracil, however, it could be useful for supportive care to improve QOL in patients for whom no standard treatment is yet available.
Aldeghi et al. ¹¹⁸	14	hepatocellular carcinoma	subcutaneous IL-2 (3 million IU/d) + po melatonin 50 mg/d	Objective tumor regressions occurred in 5 patients (complete response 1, partial response 4), with a median duration >7 months; stable disease in 6, progressive disease in 3; toxicity low in all cases; IL-2 + melatonin is a well-tolerated and effective therapy for advanced hepatocellular carcinoma.
Lissoni et al. ¹¹⁹	20	non-small cell lung cancer	melatonin begun 7 days prior to IL-2 (5 d/wk for 4 weeks)	Partial response in 4 patients, stable disease in 10, progressive disease in 6; low toxicity.
Barni et al. ¹²⁰	13	colorectal	IL-2 + melatonin	Stable disease in 4 patients, progressive disease in 9; subjective toxicity in 4.
Lissoni et al. ¹²¹	13	soft tissue	IL-2 + melatonin	Complete response in 0 patients, partial response in 1, stable disease in 8, progressive disease in 4; 6/9 with partial response or stable disease survived >1 year.
Lissoni et al. ¹²²	12	ovary	IL-2 (6 d/wk for 4 weeks) + melatonin	Complete response in 0 patients, partial response in 2, stable disease in 5, progressive disease in 5; no toxicity.
Neri et al. ¹²³	21	kidney	interferon + 10 mg melatonin at 6PM	Complete response in 3 patients, partial response in 4, stable disease in 9, progressive disease in 6; median response duration 16 months (range, 10-24 months); median survival 18 months (range, 7-24 months); 11/21 alive at 2 years.
Lissoni et al. ¹²⁴	24	solid tumors	IL-2 (6 d/wk for 4 weeks) + melatonin q/d evenings	Complete response in 0 patients, partial response in 3, stable disease (more than 6 months) in 14, progressive disease in 6; fever reported in 4 patients.
Lissoni et al. ¹²⁵	200	solid tumors	IL-2 + melatonin	Complete response in 4 patients, partial response in 36; complete response + partial response in 40/200 patients; survival >1 year in 39 percent; mild toxicity.

5-MTT: 5-methoxytryptamine; IL-2: interleukin-2; VEGF: vascular endothelial growth factor; IM: intramuscular injection.

with supportive care was found to be superior to supportive care alone in prolonging survival rate and improving performance status of patients with non-small cell lung cancer.⁵⁷ One-year survival rate was significantly higher in patients with advanced non-small cell lung cancer who were taking melatonin (20 mg/po each evening), cisplatin, and etoposide compared with those taking cisplatin and etoposide alone.⁵⁶ It was concluded that melatonin increases survival if used as an adjuvant in chemotherapy (Tables 1 and 2).

Melatonin as an antioxidant and immunomodulator

Toxic free radicals are a major cause of age-related destruction of neuronal tissue, especially the brain.⁶⁰ Melatonin is a potent antioxidant^{61,62} and is more effective than both reduced glutathione (an endogenous antioxidant) and mannitol (an antioxidant found in plants) in neutralizing the highly toxic hydroxyl radical.⁶³ It is also superior to vitamin E in neutralizing the peroxyl radical, which is produced during the oxidation of polyunsaturated acids.⁶⁴ Moreover, melatonin neutralizes the precursor of the hydroxyl radical hydrogen peroxide, resulting in a potent antioxidant chemical.^{65,66} Nitric oxide reacts with superoxide anion to form peroxynitrite, a highly toxic radical.⁶⁷ Melatonin decreases the oxidative damage of nitric oxide by inhibiting nitric oxide synthase, the rate-limiting enzyme for nitric oxide synthesis.⁶⁸

Links between the pineal gland and the brain opioid system have been documented. Both opioid peptides and melatonin play an important role in neuromodulation of the immune system. In addition, the immune dysfunctions seen in cancer depend not only on the immune system but also on altered secretion of immunomodulating neurohormones, including melatonin and

opioid peptides. Therefore, the exogenous administration of neurohormones may potentially improve the immune status in humans.⁶⁹ Melatonin can stimulate the immune response, including the anticancer immunity, and abrogate opioid-induced immunosuppression.⁷⁰ Another pineal hormone, 5-methoxytryptophol, mainly produced during the light phase of the day, has shown immunomodulation activity.^{71,72}

Melatonin seems to be an integral part of the immune system, exerting direct and indirect stimulatory effects on both cellular and humoral immunity. Melatonin enhances natural and acquired immunity in vivo and in vitro. Moreover, it can correct immunodeficiency states that may follow acute stress, viral diseases, or drug treatment.⁷³ The means by which melatonin exerts its effects on immunity have not been elucidated.⁷⁴ It does, however, appear to act through lymphocyte receptors and possibly through receptors on other immune tissues to modulate immune cells.^{75,76}

Recent studies suggest that the immunosuppressive action of inflammatory-related cytokines, mainly interleukin-6, may counteract interleukin-2 cancer immunotherapeutic effects. Melatonin may contribute to the immune reaction against cancer at least in part by removing immunosuppression related to the activation of the inflammatory response. In one pilot study, 14 patients (nine with solid tumors and five with autoimmune diseases) were treated with melatonin orally (20 mg) at 8 PM for seven days. Markers of inflammation, including erythrocyte sedimentation rate (ESR), interleukin-6, neopterin, and soluble interleukin receptor-2R, were measured. Mean serum levels of interleukin-6, neopterin, and soluble interleukin receptor-2R significantly decreased after therapy, indicating that melatonin inhibited the acute inflammatory reaction.⁷⁷ Another study measured the effects of

melatonin on T lymphocytes, natural killer cells, and eosinophils in 90 patients with advanced cancer.⁶⁹ All patients are treated with subcutaneous interleukin-2 plus melatonin (40 mg/d each night). The results were compared with those of 40 cancer patients treated with interleukin-2 alone. The mean increase in T lymphocytes, natural killer cells, and eosinophils was significantly higher in patients treated with interleukin-2 plus melatonin than in those who received interleukin-2 alone.

Melatonin and insomnia

Melatonin in doses as low as 0.3 mg to 1 mg has shown efficacy in insomnia.⁷⁸ Melatonin significantly shortens the time needed to go to sleep, decreases the number of night awakenings, and improves sleep quality and overall sleep time.^{79,80} Unlike benzodiazepines, melatonin does not suppress REM sleep or alter sleep architecture.^{81,82} In addition, melatonin enables benzodiazepine discontinuation in chronic users.⁸³ Inclusion of melatonin in cancer therapy may provide substantial benefits by enhancing nighttime sleep even in the absence of the antitumor effects. Adequate long-term studies examining both efficacy and toxicity are lacking. Further studies evaluating dose-response relationships and drug interactions are warranted.⁸⁴

Melatonin and depression

Melatonin has been proposed as a biologic marker for depression,⁸⁵ a common concomitant condition in cancer patients. A decrease in nocturnal melatonin levels has been detected in patients suffering from depression,^{86,87} and lower serum levels of melatonin have been found in patients with depression compared with healthy controls.⁸⁷⁻⁹¹ However, other studies report higher serum levels of melatonin in

patients with depression vs. healthy controls.⁹²⁻⁹⁴ More study is required to determine the role of neuroendocrine hormones including melatonin in depression.

Melatonin and thrombocytopenia

Cancer immunotherapy with interleukin-2 tends to induce thrombocytopenia. This is secondary to enhanced peripheral platelet destruction following the activation of the macrophage system by interleukin-2 itself. Preliminary data revealed normalization of platelet count after treatment with melatonin (Table 3). The melatonin effect on platelet count was investigated in 14 thrombocytopenic patients with advanced cancer.⁹⁵ Interleukin-2 (3 million IU/d) was injected subcutaneously six days a week for four weeks in association with melatonin (40 mg/d orally). Mean platelet count was significantly increased and later normalized in 10 patients. It was concluded that melatonin not only neutralized interleukin-2-induced thrombocytopenia but also increased the platelet count in thrombocytopenic patients with advanced cancer.⁹⁵ In another pilot study,⁹⁶ 20 patients with advanced cancer and persistent thrombocytopenia were given interleukin-2 and melatonin. Normal platelet count was achieved in 14 patients. Melatonin was also shown to normalize platelet count in nine out of 14 female metastatic breast cancer patients who had epirubicin-related thrombocytopenia.⁹⁷

Melatonin and hypotension

Hypotension is common in patients with advanced cancer. This may be related in part to proinflammatory cytokines. Cytokine-induced hypotension mainly depends on the stimulation of nitric oxide production—the most effective endogenous vasodilator. Melatonin inhibits nitric oxide

synthase and nitric oxide production. The latter is essential for cytokine-induced hypotension (Table 3).⁹⁸ The possible modulatory effect of melatonin on cytokine-induced cardiovascular toxicity was evaluated in 116 patients with advanced cancer receiving either interleukin-2 or tumor necrosis factor. Patients were randomized to receive melatonin (40 mg/d at 8 PM) or not. Hypotension was less frequent in patients concomitantly taking melatonin than in those who received interleukin-2 or tumor necrosis factor alone.⁹⁸

Adverse effects of melatonin

Melatonin appears to be safe. Sleepiness and fatigue are the most common adverse events. Fevers, chills, arthralgias, and myalgias are rare. Leukopenia and elevation of liver enzymes are modest and reversible.³⁹ Other possible adverse affects include inhibition of fertility, suppression of male sexual drive, hypothermia, headache, nausea, nightmares, or worsened depression.⁹⁹ No serious adverse side effects were reported after oral administration of high dose melatonin (1 g/d) for 30 days in healthy humans.¹⁰⁰ Although melatonin has proven safe thus far, it is advised that patients taking it over long periods be monitored for any potential unusual or idiosyncratic reactions.¹⁰¹

Melatonin in palliative medicine

Patients with advanced cancer are multisymptomatic. The frequency of symptoms was studied prospectively in 1,000 patients on initial referral to a large acute palliative care program.¹⁰² The median number of symptoms per patient was 11 (range, 1 to 27). The 10 most prevalent symptoms were pain, fatigue, weakness, anorexia, lack of energy, dry mouth, constipation, early satiety, dyspnea, and weight loss > 10 percent. Weight loss was reported in

50 percent, depression in 41 percent, and anxiety in 24 percent. More than 50 percent of patients had the cancer anorexia-cachexia syndrome, which is the leading cause of death in advanced cancer.

To date, no single agent has consistently improved weight, strength, QOL, body composition, and appetite in advanced cancer. Polypharmacy is an ongoing problem. The golden rule is to treat several symptoms with one drug—“the magic bullet”—with the ultimate goal of improving QOL with the fewest number of side effects. As such, melatonin seems to hold promise in palliative medicine. One may argue that melatonin is unlikely to have any major benefits in patients with advanced cancer. Although it is true that evidence of its efficacy is limited, enough randomized clinical trials, anecdotal reports, and uncontrolled clinical series exist to encourage double-blind randomized placebo-controlled trials. (The latter is not feasible in cancer patients at end of life due to ethical issues. Patients with a life expectancy of six months or less should not, in the authors' opinion, be placed in double-blind placebo-controlled trials.)

Future research and study design

Several problems face the future of melatonin research in the United States. First, melatonin is not currently categorized as a drug or regulated by the FDA. Second, melatonin research is underfunded. Third, because production is unregulated, melatonin purity and dosage accuracy is questionable, and current doses may be ineffective or may cause high plasma melatonin levels. Fourth, its side-effect profile is not well-known. Finally, more solid evidence of its efficacy in cancer treatment needs to appear in the literature.

Table 3. Clinical studies of melatonin for treatment of cachexia, thrombocytopenia, and hypotension in advanced cancer

Reference	Type	N	Diagnosis	Therapy	Conclusion
Lissoni et al. ¹²⁶	randomized controlled trial	100	solid tumors	supportive care alone or supportive care + po melatonin 20 mg/d	Weight loss >10 percent was significantly higher in patients receiving supportive care alone; serum TNF levels progressively higher in supportive care group and significantly lower ($p < 0.05$) in the melatonin + supportive-care group.
Lissoni et al. ²⁷	phase II trial	14	prostate cancer	IM triptorelin 3.75 mg/mo. + po melatonin 20 mg/d	Normalization of platelet count obtained in 3/5 patients with persistent thrombocytopenia prior to study; 50 percent decrease in prostate-specific antigen serum levels obtained in 8 patients; >1-year survival achieved in 9 patients; melatonin may improve clinical outcome in metastatic prostate cancer patients.
Lissoni et al. ⁹⁶	case series	20	solid tumors + low platelet count (expected side-effect of IL-2)	melatonin added to IL-2 and administered for 4 weeks	Normalization of platelet count in 14/20 patients (70 percent).
Lissoni et al. ⁹⁸	case series	5	kidney cancer	randomly assigned to either 17 courses of IL-2 or 16 courses of IL-2 + melatonin (10 mg/d po evenings)	Frequency of severe hypotension was significantly greater with IL-2 alone than with IL-2 + melatonin; depression more common during IL-2 alone.
Lissoni et al. ¹²⁶	case series	20	solid tumors	TNF + melatonin	No effect on anemia; thrombocytopenia reduced from 40 to 16.5 percent.
Lissoni et al. ¹²⁸	randomized controlled trial	116	solid tumors	IL-2 alone (n = 45), IL-2 + melatonin (n = 46), TNF (n = 13), TNF + melatonin (n = 12)	Hypotension significantly less frequent in patients concomitantly treated with melatonin than in those receiving either IL-2 or TNF immunotherapy alone (IL-2 11/45 vs. 2/46, $p < 0.05$; TNF 10/23 vs. 1/12, $p < 0.01$); melatonin may prevent hypotension occurring during cancer immunotherapy with IL-2 or TNF; melatonin may prevent cytokine-induced hypotension by inhibiting nitric oxide production.
Lissoni et al. ¹²⁹	case series	12	breast cancer	melatonin 7 days prior to chemotherapy and qd during at least 4 weekly cycles with epirubicin	Induction phase with melatonin induced a normalization of platelet count in 9/12 evaluable patients; no further platelet decline occurred during chemotherapy.

IL-2: interleukin-2; IM: intramuscular injection; TNF: tumor necrosis factor.

Future trials are necessary to determine whether the circadian rhythm in cancer patients is normal or abnormal prior to melatonin therapy. Long-term safety data are required to fully understand melatonin's toxicity profile. Additional research is also needed to determine the accurate therapeutic dose of melatonin and the optimal time of administration required to induce its biologic effects. Establishing its efficacy in relation to melatonin receptor expression by cancer cells and to the endogenous production of melatonin itself is a priority.

Only one study in the literature addressed the role of melatonin in cancer cachexia. In that study, melatonin (20 mg/d each night) was shown to significantly increase weight and decrease serum levels of tumor necrosis factor. Cancer-related anorexia-cachexia is the leading cause of death in patients with advanced cancer. Melatonin alone or combined with an appetite stimulant (e.g., megestrol acetate) or another anti-cytokine (e.g., thalidomide) can be investigated as a possible therapy for cancer-related cachexia. Phase II studies of melatonin's effect on cancer-related cachexia should be undertaken. Another avenue of research is to evaluate the efficacy of melatonin in improving patient-perceived QOL. Whether the primary objective is weight stabilization or QOL, research should address secondary objectives including depression, fatigue, insomnia, performance status, patient satisfaction, symptom assessment, and toxicity.

Researchers interested in conducting melatonin studies are encouraged to refer to William Hruskesky's chapter on melatonin in cancer therapy, which appears in Bartsch et al.'s, *The Pineal Gland and Cancer* (pp. 476-508).¹¹ In it, the author gives a detailed explanation of the steps necessary to achieve a well-designed study of melatonin in cancer-related fatigue. His findings support our belief that melatonin warrants further attention in palliative medicine.

Conclusion

Melatonin is the pacemaker of the circadian clock. Exposure to light at night suppresses the physiologic production of melatonin and disrupts the circadian clock. Evidence now links low serum melatonin levels and disruption of circadian rhythms to high cancer risk. Increased incidence of breast cancer and colorectal cancer has been reported in night shift workers who are exposed to light at night.

Melatonin has important therapeutic applications in oncology. Research has shown that melatonin slows disease progression and improves survival in patients with advanced cancer. Melatonin can stimulate the immune response, including the cancer immunity. It can be used either alone or to biologically modulate conventional anticancer therapies including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy.

Melatonin may play a role in cancer-related cachexia by decreasing serum levels of tumor necrosis factor, interleukin-6, and the acute inflammatory response. Biologic effects of melatonin depend upon what time of day it is made available. Despite the evidence supporting proper-timing therapy, few physicians incorporate chronotherapy in their clinical practice. Melatonin can be prescribed by a physician according to the laws of the country in which it is taken. Evidence shows that pure and regulated melatonin is effective in the treatment of advanced cancer and should be made available in the future.

Acknowledgments

We thank LuAnn Eidsness, MD, Chairwoman of Internal Medicine at University of South Dakota, and David Maddox, PhD, Director of Research at the University of South Dakota, for their continuous support of research activities among internal medicine residents.

References

1. Pang SF, Allen AE: Extra-pineal melatonin in the retina: Its regulation and physiological function. In Reiter RJ (ed.): *Pineal Research Review* (vol. 4). New York: Alan R. Liss, 1986; pp. 55-95.
2. Mhatre MC, van Jaarsveld AS, Reiter RJ: Melatonin in the lacrimal gland: First demonstration and experimental manipulation. *Biochem Biophys Res Commun.* 1988; 153: 1186-1192.
3. Tan DX, Manchester LC, Qi W, et al.: Identification of highly elevated levels of melatonin in bone marrow: Its origin and significance. *Biochim Biophys Acta.* 1999; 1472: 206-214.
4. Huether G, Poeggeler B, Reimer A, et al.: Effect of tryptophan administration on circulating melatonin levels in chicks and rats: Evidence for stimulation of melatonin synthesis and release in the gastrointestinal tract. *Life Sci.* 1991; 51: 945-953.
5. Kennaway DJ, Voultsios A: Circadian rhythm of free melatonin in human plasma. *J Clin Endocrinol Metab.* 1998; 83: 1013-1015.
6. Lucas RJ, Freedman MS, Munoz M, et al.: Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. *Science.* 1999; 284(5413): 505-507.
7. Brainard GC, Rollag MD, Hanifin JP: Photic regulation of melatonin in humans: Ocular and neural signal transduction. *J Biol Rhythms.* 1997; 12(6): 537-46.
8. Blask DE, Hill SM: Effects of melatonin on cancer: Studies on MCF-7 human breast cancer cells in culture. *J Neural Transm.* 1986; 21: 433-449.
9. Morin D, Simon N, Depres A, et al.: Melatonin high-affinity binding to alpha-1-acid glycoprotein in human serum. *Pharmacology.* 1997; 54: 271-275.
10. Nowak R, McMillen IC, Redman J, et al.: The correlation between serum and salivary melatonin concentrations and urinary 6-hydroxymelatonin sulphate excretion rates: Two non-invasive techniques for monitoring human circadian rhythmicity. *Clin Endocrinol (Oxf).* 1987; 27: 445-452.
11. Hruskesky WJM: Melatonin cancer therapy. In Bartsch C, Bartsch H, Blask DE, et al.: (eds.): *The Pineal Gland and Cancer: Neuroimmunoendocrine Mechanisms in Malignancy*. New York: Springer-Verlag, 2001; pp. 476-508.
12. Lane EA, Moss HB: Pharmacokinetics

- of melatonin in man: First pass hepatic metabolism. *J Clin Endocrinol Metab.* 1985; 61: 1214-1216.
13. Brown EN, Choe Y, Shanahan TL, et al.: A mathematical model of diurnal variations in human plasma melatonin levels. *Am J Physiol.* 1997; 272: 506-516.
14. Brydon L, Petit L, de Coppet P, et al.: Polymorphism and signaling of melatonin receptors. *Reprod Nutr Dev.* 1999; 39: 315-324.
15. Richardson G, Tate B: Hormonal and pharmacologic manipulation of the circadian clock: Recent developments and future strategies. *Sleep.* 2000; 23: S77-S82.
16. Reppert SM, Weaver DR, Rivkees SA, et al.: Putative melatonin receptors in a human biological clock. *Science.* 1988; 242: 78-81.
17. Bartsch C, Bartsch H, Fluchter SH, et al.: Evidence for modulation of melatonin secretion in men with benign and malignant tumors of the prostate: Relationship with the pituitary hormones. *J Pineal Res.* 1985; 2(2): 121-132.
18. Schernhammer ES, Laden F, Speizer FE, et al.: Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst.* 2001; 93(20): 1563-1568.
19. Schernhammer ES, Laden F, Speizer FE, et al.: Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst.* 2003; 95(11): 825-828.
20. Armstrong SM: Treatment of sleep disorders by melatonin administration. In Folds A, Reiter RJ (eds.): *Advances in Pineal Research.* London: J. Libbey and Co., 1991: pp. 263-274.
21. Hrushesky WJM: Circadian timing of cancer chemotherapy. *Science.* 1985; 228: 73-75.
22. Schmiegelow K, Glomstein A, Kristinsson J, et al.: Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. Nordic Society for Pediatric Hematology and Oncology (NOPHO). *J Pediatr Hematol Oncol.* 1997; 19(2): 102-109.
23. Levi F, Zidani R, Brienza S, et al.: A multicenter evaluation of intensified, ambulatory, chronomodulated chemotherapy with oxaliplatin, 5-fluorouracil, and leucovorin as initial treatment of patients with metastatic colorectal carcinoma. International Organization for Cancer Chronotherapy. *Cancer.* 1999; 85(12): 2532-2540.
24. Lerner AB, Case JD, Takahashi Y, et al.: Isolation of melatonin, pineal factor that lightens melanocytes. *J Amer Chem Soc.* 1958; 80: 2587.
25. Blask DE, Wilson ST, Lemus-Wilson AM: The oncostatic and oncomodulatory role of the pineal gland and melatonin. In Maestroni GJM, Conti A, Reiter RJ (eds.): *Advances in Pineal Research.* London: John Libbey, 1994: pp. 235-241.
26. Banerjee S, Margulis L: Mitotic arrest by melatonin. *Exp Cell Res.* 1973; 78: 314-318.
27. Lissoni P, Cazzaniga M, Tancini G, et al.: Reversal of clinical resistance to LHRH analogue in metastatic prostate cancer by the pineal hormone melatonin: Efficacy of LHRH analogue plus melatonin in patients progressing on LHRH analogue alone. *Eur Urol.* 1997; 31(2): 178-181.
28. Lissoni P, Rovelli F, Malugani F, et al.: Anti-angiogenic activity of melatonin in advanced cancer patients. *Neuroendocrinol Lett.* 2001; 22(1): 45-47.
29. Hu DN, Roberts JE: Melatonin inhibits growth of cultured human uveal melanoma cells. *Melanoma Res.* 1997; 7: 27-31.
30. Blask DE, Wilson ST, Zalatan F: Physiological melatonin inhibition of human breast cancer cell growth in vitro: Evidence for a glutathione-mediated pathway. *Cancer Res.* 1997; 57: 1909-1914.
31. Wilson ST, Blask DE: Melatonin augments the sensitivity of MCF-7 human breast cancer cells to tamoxifen in vitro. *J Clin Endocrinol Metab.* 1992; 75: 669-670.
32. Kikuchi Y, Kita T, Miyauchi M, et al.: Inhibition of human ovarian cancer cell proliferation in vitro by neuroendocrine hormones. *Gynecol Oncol.* 1989; 32: 60-64.
33. Cos S, Verduga R, Fernandez-Viadero C, et al.: Effects of melatonin on the proliferation and differentiation of human neuroblastoma cells in culture. *Neurosci Lett.* 1996; 216: 113-116.
34. Karasek M, Kunert-Radek J, Stepień H, et al.: Melatonin inhibits the proliferation of estrogen-induced rat pituitary tumor cells in vitro. *Neuroendocrinol Lett.* 1988; 10: 135-140.
35. Bartsch H, Bartsch C, Simon WE, et al.: Antitumor activity of the pineal gland: Effect of unidentified substances versus the effect of melatonin. *Oncology.* 1992; 49: 27-30.
36. Lissoni P, Barni S, Cazzaniga M, et al.: Efficacy of the concomitant administration of the pineal hormone melatonin in cancer immunotherapy with low-dose IL-2 in patients with advanced solid tumors who had progressed on IL-2 alone. *Oncology.* 1994; 51(4): 344-347.
37. Lissoni P, Barni S, Tancini G, et al.: Immunotherapy with subcutaneous low-dose interleukin-2 and the pineal indole melatonin as a new effective therapy in advanced cancers of the digestive tract. *Br J Cancer.* 1993; 67(6): 1404-1407.
38. Lissoni P, Barni S, Tancini G, et al.: Immunoendocrine therapy with low-dose subcutaneous interleukin-2 plus melatonin of locally advanced or metastatic endocrine tumors. *Oncology.* 1995; 52(2): 163-166.
39. Neri B, Fiorelli C, Moroni F, et al.: Modulation of human lymphoblastoid interferon activity by melatonin in metastatic renal cell carcinoma: A phase II study. *Cancer.* 1994; 73: 3015-3019.
40. Lissoni P, Vaghi M, Ardizzoia A, et al.: A phase II study of chemoneuroimmunotherapy with platinum, subcutaneous low-dose interleukin-2 and the pineal neurohormone melatonin (P.I.M.) as a second-line therapy in metastatic melanoma patients progressing on dacarbazine plus interferon-alpha. *In Vivo.* 2002; 16(2): 93-96.
41. Lissoni P, Tancini G, Barni S, et al.: Treatment of cancer chemotherapy-induced toxicity with the pineal hormone melatonin. *Support Care Cancer.* 1997; 5(2): 126-129.
42. Lissoni P, Barni S, Mandala M, et al.: Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer.* 1999; 35: 1688-1692.
43. Vijayalaxmi, Reiter RJ, Meltz ML, et al.: Melatonin: Possible mechanisms involved in its "radioprotective" effect. *Mutat Res.* 1998; 404: 187-189.
44. Maestroni GJM, Conti A: Melatonin in human breast cancer tissue: Association with nuclear grade and estrogen receptor status. *Lab Invest.* 1996; 75: 557-561.
45. Blask DE: The melatonin rhythm in cancer patients. In Shafi M (ed.): *Melatonin in Psychiatric and Neoplastic Disorders.* Washington, DC: American Psychiatric Press, 1997: pp. 257-275.
46. Bartsch C, Kvetnoy I, Kvetnaia T, et al.: Nocturnal urinary 6-sulfatoxymelatonin and proliferating cell nuclear antigen-immunopositive tumor cells show strong positive correlations in patients with gastrointestinal and lung cancer. *J Pineal Res.* 1997; 23: 90-96.
47. Blask DE, Hill SM: Melatonin and cancer: Basic and clinical perspectives. In Miles

- A, Philbrick DRS, Thompson C (eds.): *Melatonin: Clinical Perspectives*. New York: Oxford University Press, 1988: pp. 128-173.
48. Kiratli H, Gedik S, Us D, et al.: Serum melatonin levels following enucleation and transpupillary thermotherapy in patients with choroidal melanoma. *Clin Experiment Ophthalmol*. 2003; 31(6): 505-508.
49. Lissoni P, Braczkowski R, Zubelewicz B, et al.: Modulation of tumor necrosis factor-alpha (TNF-alpha) toxicity by the pineal hormone melatonin (MLT) in metastatic solid tumor patients. *Ann NY Acad Sci*. 1995; 768: 334-336.
50. Lissoni P, Paolorossi F, Tancini G, et al.: Is there a role for melatonin in the treatment of neoplastic cachexia? *Eur J Cancer*. 1996; 32: 1340-1343.
51. Lissoni P, Brivio O, Brivio F, et al.: Adjuvant therapy with the pineal hormone melatonin in patients with lymph node relapse due to malignant melanoma. *J Pineal Res*. 1996; 21: 239-242.
52. Lissoni P: Modulation of anticancer cytokines IL-2 and IL-12 by melatonin and the other pineal indoles 5-methoxytryptamine and 5-methoxytryptophol in the treatment of human neoplasms. *Ann NY Acad Sci*. 2000; 917: 560-567.
53. Clapp-Lilly KL, Smith MA, Perry G, et al.: Melatonin reduces interleukin secretion in amyloid-beta stressed mouse brain slices. *Chem Biol Interact*. 2001; 134(1): 101-107.
54. Neri B, de Leonardis V, Gemelli MT, et al.: Melatonin as biological response modifier in cancer patients. *Anticancer Res*. 1998; 18(2B): 1329-1332.
55. Lissoni P, Barni S, Tancini G, et al.: Clinical study of melatonin in untreatable advanced cancer patients. *Tumori*. 1987; 73: 475-480.
56. Reiter RJ: Oxidative processes and antioxidative defence mechanisms in the aging brain. *FASEB J*. 1995; 9(7): 526-533.
57. Lissoni P, Barni S, Ardizzoia A, et al.: Randomized study with the pineal hormone melatonin versus supportive care alone in advanced nonsmall cell lung cancer resistant to a first-line chemotherapy containing cisplatin. *Oncology*. 1992; 49(5): 336-339.
58. Lissoni P, Meregalli S, Nasetto L, et al.: Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. *Oncology*. 1996; 53(1): 43-46.
59. Lissoni P, Paolorossi F, Ardizzoia A, et al.: A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state. *J Pineal Res*. 1997; 23(1): 15-19.
60. Marshall KA, Reiter RJ, Poeggeler B, et al.: Evaluation of the antioxidant activity of melatonin in vitro. *Free Radic Biol Med*. 1996; 21: 307-315.
61. Chan TY, Tang PL: Characterization of the antioxidant effects of melatonin and related indoleamines in vitro. *J Pineal Res*. 1996; 20: 187-191.
62. Tan DX, Manchester LC, Reiter RJ, et al.: A novel melatonin metabolite, cyclic 3-hydroxymelatonin: A biomarker of in vivo hydroxyl radical generation. *Biochem Biophys Res Comm*. 1998; 253: 614-620.
63. Poeggeler B, Reiter RJ, Tan DX, et al.: Melatonin, hydroxyl radical-mediated oxidative damage and aging: A hypothesis. *J Pineal Res*. 1993; 14: 151-168.
64. Tan DX, Manchester LC, Reiter RJ, et al.: Melatonin directly scavenges hydrogen peroxide: A potentially new metabolic pathway of melatonin biotransformation. *Free Radic Biol Med*. 2000; 29: 1177-1185.
65. Barlow-Walden LR, Reiter RJ, Abe A, et al.: Melatonin stimulated brain glutathione peroxidase activity. *Neurochem Int*. 1995; 26: 497-502.
66. Blanchard B, Pompon D, Ducrocq C: Nitrosation of melatonin by nitric oxide and peroxynitrite. *J Pineal Res*. 2000; 29: 184-192.
67. Pozo D, Reiter RJ, Calvo JR, et al.: Inhibition of cerebellar nitric oxide synthase and cyclic GMP production by melatonin via complex formation with colmodulin. *J Cell Biochem*. 1997; 65: 430-442.
68. Lissoni P, Barni S, Tancini G, et al.: Pineal-opioid system interactions in the control of immunoinflammatory responses. *Ann NY Acad Sci*. 1994; 741: 191-196.
69. Lissoni P, Mandala M, Brivio F: Abrogation of the negative influence of opioids on IL-2 immunotherapy of renal cell cancer by melatonin. *Eur Urol*. 2000; 38(1): 115-118.
70. Maestroni GJM: The immunoneuroendocrine role of melatonin. *J Pineal Res*. 1993; 14: 1-10.
71. Lissoni P, Fumagalli L, Paolorossi F, et al.: Anticancer neuroimmunomodulation by pineal hormones other than melatonin: Preliminary phase II study of the pineal indole 5-methoxytryptophol in association with low-dose IL-2 and melatonin. *J Biol Regul Homeost Agents*. 1997; 11 (3): 119-122.
72. Lissoni P, Barni S, Meregalli S, et al.: Modulation of cancer endocrine therapy by melatonin: A phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone. *Br J Cancer*. 1995; 71: 854-856.
73. Fraschini F, Demartini G, Esposti D, et al.: Melatonin involvement in immunity and cancer. *Biol Signals Recept*. 1998; 7(1): 61-72.
74. Zhang Z, Insera PF, Liang B, et al.: Melatonin, immune modulation and aging. *Autoimmunity*. 1997; 26(1): 43-53.
75. Guerrero JM, Garcia-Maurino S, Pozo D, et al.: Mechanisms involved in the immunomodulatory effects of melatonin on the human immune system. In Bartsch C, Bartsch H, Blask D, et al. (eds.): *The Pineal Gland and Cancer*. Heidelberg, Germany: Springer-Verlag, 2001: pp. 408-416.
76. Lissoni P, Barni S, Ardizzoia A, et al.: Randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastases due to solid neoplasms. *Cancer*. 1994; 73(3): 699-701.
77. Skene DJ, Swaab DF: Melatonin rhythmicity: Effect of age and Alzheimer's disease. *Exp Gerontol*. 2003; 38(1-2): 199-206.
78. Zhdanova IV, Wurtman RJ, Lynch HJ, et al.: Sleep-inducing effects of low-doses of melatonin ingested in the evening. *Clin Pharmacol Ther*. 1995; 57: 552-558.
79. Waldbauser F, Saletu B, Trinchard-Lugan I: Sleep laboratory investigations on hypnotic properties of melatonin. *Psychopharmacology*. 1990; 100(2): 222-226.
80. Naguib M, Samarkandi AH: Pre-medication with melatonin: A double blind, placebo-controlled comparison with midazolam. *Br J Anaesth*. 1999; 82: 875-880.
81. Olde Rikkert MG, Rigaud AS: Melatonin in elderly patients with insomnia: A systematic review. *Z Gerontol Geriatr*. 2001; 34(6): 491-497.
82. Zisapel N: The use of melatonin for the treatment of insomnia. *Biol Signals Recept*. 1999; 8(1-2): 84-89.
83. Chase JE, Gidal BE: Melatonin: Therapeutic use in sleep disorders. *Ann Pharmacother*. 1997; 31(10): 1218-1226.
84. Brown GM: Neuroendocrine probes as biological markers of affective disorders:

- New directions. *Can J Psychiatry*. 1989; 34(8): 819-823.
85. Brown RP, Kocsis JH, Caroff S, et al.: Depressed mood and reality disturbance correlate with decreased nocturnal melatonin in depressed patients. *Acta Psychiatr Scand*. 1987; 76(3): 272-275.
86. Shafii M, MacMillan DR, Key MP, et al.: Nocturnal serum melatonin profile in major depression in children and adolescents. *Arch Gen Psychiatr*. 1996; 53(11): 1009-1013.
87. Beck-Friis J, Ljunggren JG, Thoren M, et al.: Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. *Psychoneuroendocrinology*. 1985; 10(2): 173-186.
88. McIntyre IM, Judd FK, Marriott PM, et al.: Plasma melatonin levels in affective states. *Int J Clin Pharmacol Res*. 1989; 9(2): 159-164.
89. Brown RP, Kocsis JH, Caroff S, et al.: Depressed mood and reality disturbance correlate with decreased nocturnal melatonin in depressed patients. *Acta Psychiatr Scand*. 1987; 76(3): 272-275.
90. Brown R, Kocsis JH, Caroff S, et al.: Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *Am J Psychiatry*. 1985; 142(7): 811-816.
91. Rubin RT, Heist EK, McGeoy SS, et al.: Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. *Arch Gen Psychiatry*. 1992; 49(7): 558-567.
92. Claustrat B, Chazot G, Brun J, et al.: A chronobiological study of melatonin and cortisol secretion in depressed subjects: Plasma melatonin, a biochemical marker in major depression. *Biol Psychiatry*. 1984; 19(8): 1215-1228.
93. Szymanska A, Rabe-Jablonska J, Karasek M: Diurnal profile of melatonin concentrations in patients with major depression: Relationship to the clinical manifestation and antidepressant treatment. *Neuroendocrinol Lett*. 2001; 22(3): 192-198.
94. Lissoni P, Barni S, Brivio F, et al.: Treatment of cancer-related thrombocytopenia by low-dose subcutaneous interleukin-2 plus the pineal hormone melatonin: A biological phase II study. *J Biol Regul Homeost Agents*. 1995; 9(2): 52-54.
95. Lissoni P, Barni S, Brivio F, et al: A biological study on the efficacy of low-dose subcutaneous interleukin-2 plus melatonin in the treatment of cancer-related thrombocytopenia. *Oncology*. 1995; 52(5): 360-362.
96. Lissoni P, Tancini G, Paolorossi F, et al.: Chemoneuroendocrine therapy of metastatic breast cancer with persistent thrombocytopenia with weekly low-dose epirubicin plus melatonin: A phase II study. *J Pineal Res*. 1999; 26(3): 169-173.
97. Lissoni P, Pittalis S, Ardizzoia A, et al.: Prevention of cytokine-induced hypotension in cancer patients by the pineal hormone melatonin. *Support Care Cancer*. 1996; 4(4): 313-316.
98. Lissoni P, Brivio F, Barni S, et al.: Neuroimmunotherapy of human cancer with interleukin-2 and the neurohormone melatonin: Its efficacy in preventing hypotension. *Anticancer Res*. 1990; 10(6): 1759-1761.
99. Sebra MLV, Bignotto M, Pinto LR Jr, et al.: Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res*. 2000; 29: 193-200.
100. McArthur AJ, Budden SS: Sleep dysfunction in Rett syndrome: A trial of exogenous melatonin treatment. *Dev Med Child Neurol*. 1998; 40: 186-192.
101. Lissoni P, Paolorossi F, Tancini G, et al.: A phase II study of tamoxifen plus melatonin in metastatic solid tumour patients. *Br J Cancer*. 1996; 74(9): 1466-1468.
102. Walsh D, Donnelly S, Rybicki L: The symptoms of advanced cancer: Relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer*. 2000; 8(3): 175-179.
103. Lissoni P, Barni S, Tancini G, et al.: Immunotherapy with subcutaneous low-dose interleukin-2 and the pineal indole melatonin as a new effective therapy in advanced cancers of the digestive tract. *Br J Cancer*. 1993; 67(6): 1404-1407.
104. Barni S, Lissoni P, Cazzaniga M, et al.: A randomized study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. *Oncology*. 1995; 52(3): 243-245.
105. Lissoni P, Barni S, Mandala M, et al.: Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer*. 1999; 35(12): 1688-1692.
106. Lissoni P, Barni S, Ardizzoia A, et al.: A randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastases due to solid neoplasms. *Cancer*. 1994; 73(3): 699-701.
107. Lissoni P, Meregalli S, Nosetto L, et al.: Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. *Oncology*. 1996; 53(1): 43-46.
108. Lissoni P, Barni S, Cattaneo G, et al.: Clinical results with the pineal hormone melatonin in advanced cancer resistant to standard antitumor therapies. *Oncology*. 1991; 48(6): 448-450.
109. Lissoni P, Barni S, Fossati V, et al.: A randomized study of neuroimmunotherapy with low-dose subcutaneous interleukin-2 plus melatonin compared to supportive care alone in patients with untreatable metastatic solid tumour. *Support Care Cancer*. 1995; 3(3): 194-197.
110. Lissoni P, Rovelli F, Frassinetti A, et al.: Oncostatic activity of pineal neuroendocrine treatment with the pineal indoles melatonin and 5-methoxytryptamine in untreatable metastatic cancer patients progressing on melatonin alone. *Neuroendocrinol Lett*. 2000; 21(4): 319-323.
111. Lissoni P, Mandala M, Brivio F: Abrogation of the negative influence of opioids on IL-2 immunotherapy of renal cell cancer by melatonin. *Eur Urol*. 2000; 38(1): 115-118.
112. Cerea G, Vaghi M, Ardizzoia A, et al.: Biomodulation of cancer chemotherapy for metastatic colorectal cancer: A randomized study of weekly low-dose irinotecan alone versus irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. *Anticancer Res*. 2003; 23(2C): 1951-1954.
113. Lissoni P, Barni S, Tancini G, et al.: Immunotherapy with subcutaneous low-dose interleukin-2 and the pineal indole melatonin as a new effective therapy in advanced cancers of the digestive tract. *Br J Cancer*. 1993; 67(6): 1404-1407.
114. Lissoni P, Barni S, Cattaneo G, et al.: Clinical results with the pineal hormone melatonin in advanced cancer resistant to standard antitumor therapies. *Oncology*. 1991; 48(6): 448-450.

115. Lissoni P, Brivio F, Ardizzioia A, et al.: Subcutaneous therapy with low-dose interleukin-2 plus the neurohormone melatonin in metastatic gastric cancer patients with low performance status. *Tumori*. 1993; 79(6): 401-404.
116. Lissoni P, Bolis S, Brivio F, et al.: A phase II study of neuroimmunotherapy with subcutaneous low-dose IL-2 plus the pineal hormone melatonin in untreatable advanced hematologic malignancies. *Anticancer Res*. 2000; 20(3B): 2103-2105.
117. Barni S, Lissoni P, Paolorossi F, et al.: A study of the pineal hormone melatonin as a second line therapy in metastatic colorectal cancer resistant to fluorouracil plus folates. *Tumori*. 1990; 76(1): 58-60.
118. Aldeghi R, Lissoni P, Barni S, et al.: Low-dose interleukin-2 subcutaneous immunotherapy in association with the pineal hormone melatonin as a first-line therapy in locally advanced or metastatic hepatocellular carcinoma. *Eur J Cancer*. 1994; 30A(2): 167-170.
119. Lissoni P, Tisi E, Barni S, et al.: Biological and clinical results of a neuroimmunotherapy with interleukin-2 and the pineal hormone melatonin as a first line treatment in advanced non-small cell lung cancer. *Br J Cancer*. 1992; 66(1): 155-158.
120. Barni S, Lissoni P, Cazzaniga M, et al.: Neuroimmunotherapy with subcutaneous low-dose interleukin-2 and the pineal hormone melatonin as a second-line treatment in metastatic colorectal carcinoma. *Tumori*. 1992; 78(6): 383-387.
121. Lissoni P, Barni S, Ardizzioia A, et al.: Immunotherapy with low dose interleukin-2 in association with melatonin as salvage therapy for metastatic soft tissue sarcomas. *Oncology Rep*. 1997; 4(1): 157-159.
122. Lissoni P, Ardizzioia A, Barni S, et al.: Immunotherapy with subcutaneous low dose interleukin-2 plus melatonin as salvage therapy of heavily chemotherapy-penetrated ovarian cancer. *Oncology Rep*. 1996; 3(5): 947-949.
123. Neri B, Fiorelli C, Moroni F, et al.: Modulation of human lymphoblastoid interferon activity by melatonin in metastatic renal cell carcinoma. A phase II study. *Cancer*. 1994; 73(12): 3015-3019.
124. Lissoni P, Barni S, Rovelli F, et al.: Neuroimmunotherapy of advanced solid neoplasms with single evening subcutaneous injection of low-dose interleukin-2 and melatonin: Preliminary results. *Eur J Cancer*. 1993; 29A(2): 185-189.
125. Lissoni P, Aridizzioia A, Barni S, et al.: Efficacy and tolerability of cancer neuroimmunotherapy with subcutaneous low-dose interleukin-2 and the pineal hormone melatonin: A progress report of 200 patients with advanced solid neoplasms. *Oncology Rep*. 1995; 2(6): 1063-1068.
126. Lissoni P, Paolorossi F, Tancini G, et al.: Is there a role for melatonin in the treatment of neoplastic cachexia? *Eur J Cancer*. 1996; 32A(8): 1340-1343.
127. Braczkowski R, Zubelewicz B, Romanowski W, et al.: Modulation of tumor necrosis factor-alpha (TNF-alpha) toxicity by the pineal hormone melatonin (MLT) in metastatic solid tumor patients. *Ann NY Acad Sci*. 1995; 768: 334-336.
128. Lissoni P, Pittalis S, Ardizzioia A, et al.: Prevention of cytokine-induced hypotension in cancer patients by the pineal hormone melatonin. *Support Care Cancer*. 1996; 4(4): 313-316.
129. Lissoni P, Tancini G, Paolorossi F, et al.: Chemoneuroendocrine therapy of metastatic breast cancer with persistent thrombocytopenia with weekly low-dose epirubicin plus melatonin: A phase II study. *J Pineal Res*. 1999; 26(3): 169-173.

American Journal of Hospice & Palliative Medicine®

As we move into our 23rd year of publication, *American Journal of Hospice & Palliative Medicine* continues its long and respected tenure as the journal of record for hospice and palliative medicine. It provides an essential forum for articles covering all aspects of hospice and palliation from the medical and pharmaceutical to the administrative and social. Peer-reviewed by an internationally recognized editorial review board, *American Journal of Hospice & Palliative Medicine* is renowned worldwide for its comprehensive view of the changing focus of hospice and palliation. Indexed in Index Medicus/Medline, Leeds Medical Information and Ageline Database.

Visit our Web site for the following information:

- Current Table of Contents
- Editorial Review Board
- Subscription Information and Order Form
- Abstracts
- Cumulative Indices
- Manuscript Submission Guidelines
- Contact Information

