Review

Clinical uses of melatonin: evaluation of human trials on cancer treatment

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ABSTRACT

Melatonin is a molecule with numerous properties, which are applicable to the treatment of different types of cancers. Experimental *in vitro* and *in vivo* studies conducted with human cancer cells or animal models of carcinogenesis, have shown that melatonin enhances apoptosis and inhibits cell proliferation of several human cancer cells, reduces tumor growth rate and its metastases, reduces the side effects of chemotherapy and radiotherapy, decreases the resistance to standard cancer treatments, and potentiates the therapeutic effects of other conventional therapies. These satisfactory results obtained from "bench" need to be studied in clinical trials to verify whether they are applicable to "bedside". In this article we review the clinical trials carried out in the last 25 years which are focused on the therapeutic use of melatonin in cancer treatment. We conclude that melatonin is an effective adjuvant drug to practically any conventional cancer therapy since it is capable of improving the quality of life of patients, by normalizing sleep and alleviating general symptoms associated with tumor disease and treatment such as pain, asthenia, anorexia, etc. In the particular case of hormone-dependent breast cancer, melatonin's antiestrogenic properties make this indoleamine ideally suited for use in association with other synthetic anti-estrogen agents, as melatonin increases their efficacy while reducing their undesirable effects. Furthermore, melatonin could be an appropriate co-treatment for preventive treatment of breast cancer in people with elevated risk for this kind of neoplasia.

Keywords: melatonin, cancer therapy, anticancer drugs.

1. INTRODUCTION

Ever since the isolation of melatonin as the main secretory product of the pineal gland (1), although other tissues, including retina, gastrointestinal tract, etc. also secrete melatonin (2), hundreds of *in vitro* as well as *in vivo* experiments have described the antitumor properties of this molecule, particularly in the case of hormone-dependent mammary tumors (3-7). This is a recurring theme in the literature related to the medical publications about melatonin (8-10). The possible mechanisms involved in the anticancer action of this neurohormone have also been widely studied (11-13). Less well known is the fact that, before the discovery of melatonin, studies based on techniques of pinealectomy or the administration of pineal extracts in different animal models had, a century ago, foretold the antitumor effects of this gland (14). Despite numerous descriptions of melatonin`s promising antitumor effect, especially from *in*

vitro experiments carried out with human cancer cells or animal models of carcinogenesis, these results have not evolved "from bench to bed" as would normally been expected, and the clinical use of melatonin in cancer therapy has not lived up to the success promised by the basic research results.

Several years ago, we revised the state of art for the general clinical uses of melatonin (15), as was as its use in the treatment of specific diseases, including pediatric pathologies (16), or neurological diseases and mental and behavioral disorders (17). Presently, our objective is to review the clinical trials carried out in recent years focusing on the therapeutic use of melatonin in cancer treatment. We consider that it is high time to analyze the clinical trials carried out during the last 25 years, and, from this analysis, to reach a conclusion regarding the usefulness of melatonin in cancer therapy. In this article we will only review clinical studies that focus on the therapeutic use of melatonin in the treatment of different kinds of cancer. There are numerous reviews of experimental data supporting the anticancer properties of melatonin (5, 6, 18-21) and this information is not repeated here. Only relevant or recently published non-clinical data useful for understanding the role of melatonin as an anticancer drug will be included in this article.

For each type of tumor, we will focus our attention, if it is possible, on four aspects of the possible therapeutic uses of melatonin: a) to prevent or reduce the risk of the development of several kinds of cancer; b) to exert direct antitumor effects (i.e. reduction of tumor growth rate and/or its metastases) either alone or in combination with other drugs; c) to reduce the side effects of classical therapies such as chemotherapy and radiotherapy, and d) to improve the quality of life of cancer patients by counteracting some of the symptoms associated with the tumor processes, such as sleep disturbances or alterations of circadian rhythmicity.

2. CLINICAL TRIALS CARRIED OUT TO ASSESS THE USEFULNESS OF MELATONIN IN THE TREATMENT OF DIFFERENT NEOPLASIAS

2.1. Head and neck cancers.

Clinical trials relating to these kinds of tumors have focused solely on the possible value of melatonin in counteracting the side effects of classical treatments. Head and neck cancer patients treated with radiation develop oral mucositis, which causes pain that makes the continuation of treatment difficult, thus worsening the prognosis of the patients. A randomized, double-blind, placebo-controlled clinical trial, involving thirty-nine head and neck cancer patients, was carried out by Onseng (22). The patients received chemoradiation and melatonin (20 mg) or placebo before each irradiation, and nightly during the seven weeks of chemoradiation. The conclusion of the trial was that melatonin treatment delayed the onset of oral mucositis, thus allowing longer uninterrupted treatments as well as a reduction in the amount of analgesics prescribed and a better quality of life for the patients. The efficacy of melatonin gel for the treatment of oral mucositis has been also studied (23) and, a clinical trial of melatonin oral gel for the prevention and treatment of oral mucositis in patients with head and neck cancer who are undergoing chemoradiation is currently being conducted (EudraCT Number: 2015-001534-13).

2.2. Hepatocellular carcinoma.

The risk for hepatocellular carcinoma (HCC) and hepatic cancer metastasis has recently been related to melatonin receptor gene polymorphisms (24). *In vitro* studies with human hepatic cancer cells demonstrate that melatonin enhances apoptosis and inhibits cell proliferation, motility, and invasiveness, by acting through members of the MAPK family (25).

These basic data suggest that melatonin may play a role in the pathogenesis of HCC and can thus be used as a therapeutic target for its treatment. Furthermore, three recent articles (26-28) describe the antiproliferative and pro-apoptotic activity of melatonin in human hepatocellular carcinoma cells *in vitro*. These authors have also demonstrated that melatonin potentiates the cytotoxic effects of Sorafenib, an inhibitor of multiple tyrosine kinases which is the only effective therapy for advanced HCC, but which has limitations in its use due to the development of resistance. The combination of both drugs, melatonin and Sorefenib, synergistically activates the JNK/c-jun pathway, thus inducing the apoptosis of HCC cells. Based on these results, cotreatment with melatonin and Sorafenib could potentially offer a new therapy for patients with HCC. However, this possibility has not been clinically assayed.

We found only one clinical trial regarding the use of melatonin as an adjuvant treatment for these kinds of tumors. One hundred patients suffering inoperable advanced HCC were treated with transcatheter arterial chemoembolization associated with melatonin (20 mg/day at 8:00, 7 days before chemoembolization) or placebo. Melatonin protected these patients' liver function from the damage caused by chemoembolization and increased the survival rate of these patients (29).

2.3. Colorectal cancer.

Chemotherapy with 5-fluorouracil (5-FU) is the standard treatment for advanced colorectal cancer (CRC). However, the development of resistance to this drug results in a poor therapeutic response. For this reason, recently, numerous research efforts have been expended attempting to find a way to reduce the body's resistance to 5-FU. Some of these studies have concluded that melatonin may serve to potentiate the therapeutic effects of 5-FU and to reduce chemoresistance (30, 31). Melatonin is also effective at enhancing the response to ionizing radiation (32) and to other chemotherapy drugs such as oxaliplatin (33) as well as producing apoptosis (34, 35).

As far as we know, only Lissoni´s group has carried out clinical trials using melatonin as an adjuvant to chemotherapy treatments. Patients diagnosed with colorectal cancer and treated with oxaliplatin plus 5-FU, or irinotecan plus 5-FU and folic acid were randomly assigned to receive an adjuvant treatment with melatonin (20 mg/day, 75 patients) or placebo (77 patients). Those patients treated with chemotherapy plus melatonin showed a significantly higher overall tumor regression rate and a higher survival rate than that of patients treated with chemotherapy alone (36). In a previous study from the same research group, 30 patients with metastatic CRC, after a preliminary chemotherapeutic treatment with 5-FU, were treated, at random, with irinotecan alone or associated with melatonin (20 mg/day taken during the night). The authors concluded that, among the patients treated with melatonin, the percentage of disease-control achieved was higher than among those treated with chemotherapy alone. However, only a partial response was achieved in 5 of 14 patients treated with chemotherapy plus melatonin (37).

2.4. Gastric cancer.

Gastric cancer (GC) is the third leading cause of cancer-related death. Basic studies considering the usefulness of melatonin in the treatment of GC were revised by Asghari *et al*. (38). The mechanisms involved in the *in vitro* oncostatic effects of melatonin on human GC cells have recently been deciphered. Melatonin induces cell cycle arrest and downregulates CDC25A, phospho-CDC25A, p21 and phospho-p21. Furthermore, melatonin upregulates Bax, downregulates Bcl-xL, increases p53, and activates caspase-3 inducing apoptosis (39).

Only one clinical study was found recently, which focuses on the role of melatonin as an adjuvant drug for GC treatment. Patients suffering from GC who were treated with chemotherapy (Cisplatin + Epirubicin + Leucovorin + 5-FU) were randomly assigned for a complementary treatment with melatonin (20 mg/day, 37 cases) or placebo (34 patients), beginning 7 days before chemotherapy and taken daily until disease progression. Patients receiving melatonin showed better tolerance and response to chemotherapy, as well as a better survival-rate (36).

2.5. Pancreatic cancer.

Pancreatic ductal adenocarcinoma (PAC) is one of the most lethal malignant tumors due to the practically absence of early symptoms and its poor response to treatment with conventional chemotherapies. The role of melatonin in the pancreatic physiology including the stimulation of pancreatic enzymes secretion, by activating both the entero-pancreatic reflex and the release of cholecystokinin, as well as the prevention of pancreatic damages resulting from acute pancreatitis has been reported (40, 41).

In PAC cells, melatonin and *N*¹-acetyl-*N*¹-formyl-5-methoxykynuramine (AFMK, a melatonin metabolite) activates apoptosis and stimulates heat shock proteins (41). The effects of melatonin on PAC cells and the mechanisms involved in these effects have recently been reviewed (42).

Melatonin decreases cell viability, colony formation, cell migration and invasiveness, while increasing the apoptosis of human pancreatic carcinoma cells by inhibiting NF-κB p65 activation (43). As mentioned in the hepatocellular carcinoma section above, melatonin potentiates the anticancer activity of Sorafenib, a tyrosine kinase inhibitor. The combination of the two drugs has been proposed as a therapeutic strategy for treating PDAC (44) although there are as yet no clinical studies to this possible treatment option.

2.6. Prostate cancer.

A relationship between low melatonin production and an elevated risk of prostate cancer has been suggested by two recent studies (45, 46). The first one, a case-cohort study of 928 men without prostate cancer showed that those with low morning urinary concentration of aMT6s (a urinary metabolite of melatonin used as a representative indicator of the amount of melatonin secretion) had increased risk for advanced disease compared with men with values above the median (45). The second is a comparative study of urinary aMT6 and cortisol excretions among 120 men diagnosed with prostate cancer and 240 age-matched control subjects. The result was that patients with low aMT6 levels or a low aMT6/cortisol ratio were more prone to developing prostate cancer or advanced stage prostate cancer (46). Based on these facts, the usefulness of melatonin in the treatment of prostate cancer has been proposed.

Another recent basic study carried out by Liu *et al*. (47) described how melatonin, by binding to the MT_1 receptors of prostate cancer cells, inhibited NF-κB activation, exerting antiproliferative effects, a fact that could be used to delay the development of castration resistance in advanced prostate cancer. However, melatonin alone or in combination with ADT has not been clinically assayed in relation to prostate cancer.

Several meta-analysis of randomized trials have concluded that melatonin significantly reduces the side effects of chemotherapy, radiotherapy, supportive therapy, and palliative therapy in cancer patients, decreasing asthenia, leucopenia, nausea and vomiting, hypotension, or thrombocytopenia (48).

2.7. Ovarian cancer.

Among gynecological cancers, ovarian cancer (OC) has the highest mortality rate. The development of chemoresistance to the standard treatments based on platinum and taxanes is the main limiting factor for these kinds of treatments.

As described before in other kinds of tumors, a relationship between the circulating levels of melatonin and the risk of OC has been suggested; the serum concentrations of melatonin in women with ovarian cancer are significantly lower than in healthy women (49). On this basis, treatment with this indoleamine has been considered as a promising adjuvant therapy for OC (50). However, up to now, no clinical trials have been conducted to confirm or discredit this hypothesis.

2.8. Breast cancer.

Breast cancer (BC), and especially hormone-dependent mammary tumors, is the type of neoplasias which has been most extensively studied in relation to melatonin. Basic studies on this subject have been analyzed in numerous reviews (5, 18, 20, 51-53). However, regarding the possible direct therapeutic effects of melatonin in breast cancer, as far as the authors are aware, only one clinical trial has been published, and this study was focused on the evolution of women undergoing a previous conventional treatment rather than on the use of melatonin as a primary treatment. This was a randomized, double blind, placebo controlled trial carried out in postmenopausal breast cancer (stages 0-III) survivors who had completed a standard treatment protocol that included hormonal therapy. The women were treated with melatonin (3 mg/day, orally, for 4 months) or placebo (48 and 47 patients, respectively). The authors did not find any significant effects of melatonin supplementation on the studied plasma cancer biomarkers (estradiol, IGF-1, IGFBP-3 and IGF-1/ IGFBP-3 quotient) (54).

Melatonin has been demonstrated to have simultaneous properties of selective estrogen enzyme modulators (SEEM) and selective estrogen receptor modulators (SERM) (53-57). Furthermore, melatonin increases the sensitivity of MCF-7 cells to the effects of tamoxifen, an antiestrogen agent widely used in the treatment of ER+ breast cancer (60). Melatonin also increases the effects of antiaromatase drugs used in clinic (61). Although this evidence supports the usefulness of melatonin as a means of enhancing the efficiency of conventional SEEM and SERM drugs, up to now, we have not noticed any of clinical assays to check this hypothesis

In our opinion, the possible use of melatonin in BC prevention for people with an elevated risk of this malignance is particularly relevant (3, 62). Among the factors of BC risk listed by the National Cancer Institute, some of them seem especially appropriate for prevention with melatonin. The association between hormone replacement-therapy (HRT) and breast cancer risk is still a subject of debate (63, 64). Several randomized trials, such as the Women's Health Initiative (WHI) (1997) (65), showed an increased risk of breast cancer among women receiving HRT with estrogens plus progesterone dependent on the dose as well as the duration of treatment. However, other studies conclude that the increased risk of BC after HRT is small or not significant (64). Based on its known SERM and SEEM properties, melatonin could be used to reduce the BC risk after HRT. With this purpose, an association of melatonin with conventional estrogens and progesterone has been patented (66) as a new formulation for HRT to reduce the possible risk of BC.

Obesity is another risk factor for BC among postmenopausal women (65). Melatonin might be used to reduce the BC risk associated with obesity because, in animal models, it prevents against obesity (68, 69) and reduces the expression and activity of aromatase, thus decreasing the synthesis of estrogens by adipose tissue (70-71).

In recent years, the role of environmental factors in BC risk has received increased

consideration (72). Exposure to light-at-night inhibits melatonin secretion and induces chronodisruption, two factors that, in animal experiments, have been demonstrated to accelerate the growth of mammary tumors (73, 74). Women engaged in nocturnal work have an increased risk of BC (75), a risk that could be reduced by treatment with melatonin. Also listed among the environmental factors of BC risk is the exposure to chemical contaminants, particularly those contaminants exhibiting estrogenic properties: the xenoestrogens. Women working in contact with xenoestrogens (e.g. cadmium used in manufactures of nickel/cadmium batteries) also have an elevated BC risk that could be reduced with melatonin. The efficacy of this indoleamine at counteracting the effects of xenoestrogens *in vivo* and *in vitro* has been experimentally demonstrated (76-79). At present, clinical assays to evaluate the utility of melatonin in BC prevention are non-existent.

The usefulness of melatonin as an adjuvant drug to prevent or reduce the side effects of SERM and SEEM drugs used in BC treatment is probably the most studied clinical application of this indoleamine. Osteoporosis is a side effect of antiaromatases that could be prevented by melatonin. Melatonin promotes osteoblast proliferation and the synthesis of osteoprotegerin thus inhibiting bone resorption and increasing bone mass (80-83). Based on this data, several clinical trials were carried out in women with postmenopausal osteopenia and have concluded that administering melatonin (1-3 mg/day for 6-12 months) improved bone mineral density and decreased the risk of fractures (84, 85). However simultaneous treatment with melatonin and antiaromatase in BC has not yet been assayed. In animal models, melatonin reduces the hepatotoxicity of aromatase inhibitors like letrozole (53). A hybrid compound of melatonin and tamoxifen (*N*-desmethyl-4-hydroxytamoxifen-melatonin) has been patented (US8785501) (66, 86) in order to combine the antiestrogenic properties of both molecules and to reduce the undesirable side effects of tamoxifen, such as the risk of uterine hyperproliferation.

2.9. Melanoma.

The evidence supporting the use of melatonin in the treatment of skin cancer has recently been revised (87). In experiments carried out in mice carrying human melanoma xenografts, melatonin enhances the antitumor effect of Vemurafenib (a selective inhibitor of BRAF kinase) and reduces its toxicity. These results suggest a potential use for this indoleamine as an adjuvant drug in melanoma treatment (88).

Regarding melanoma treatment, several clinical studies have assayed the association of melatonin with other molecules (IL-2, interferon alpha, platinum, etc.). However, although melatonin was in all cases well tolerated, the results of these trials do not support a relevant role for melatonin in the treatment of this kind of skin tumors (89, 90).

Melatonin creams or placebo were used in a randomized, placebo-controlled, double-blind study in 23 healthy volunteers to assess their protective effect against erythema induced by sunlight. The conclusion of the trial was that 12.5% melatonin cream protects against the UV radiation resulting from exposure to sunlight, considered the main etiology for melanoma (91).

2.10. Hematologic and lymphatic malignancies.

Hematological neoplasms, including leukemias, lymphomas and multiple myelomas, are the principal cause of cancer related mortality in children and adolescents around the world. The theoretical basis of the possible utility of melatonin in the treatment of these kinds of malignancies has recently been revised (92). In that review, the authors emphasized the coincidence of low serum melatonin levels, whatever its cause, with an elevated risk of myeloid tumors and lymphoma. However, regarding clinical trials, only a few assays have been carried

out, all of them in Italy, by the same research group, and using melatonin as one of the ingredients of a cocktail of drugs. In one of these trials, twenty patients diagnosed with non-Hodgkin´s lymphomas (low grade, stage III or IV) received a drug cocktail including cyclophosphamide, bromocriptine, retinoids, melatonin (given orally, at a dose of 20 mg/day: 10 mg at 2 pm and again at 9 pm) and ACTH. The treatment lasted for one month and was prolonged for a further two months in those patients undergoing stable or improved disease symptoms. The treatment was effective, and 70% of the patients experienced at least a partial improvement (93). The same combination of drugs was also applied to a patient experiencing a relapse of high-grade non-Hodgkin's lymphoma after autologous stem cell transplantation performed 2 years earlier, obtaining a complete remission (94), and to another patients with low-grade non-Hodgkin's lymphoma at an advanced stage, also resulting in a complete remission (95). The last clinical assay published by this group was carried out on 4 patients with chronic lymphocytic leukemia (progressive stage I). Patients received the same combination of drugs mentioned above which included melatonin. In all cases, a partial remission was observed after 8 weeks of treatment and the treatment was continued until the patients registered lymphocyte counts below 4000/ml. The patients did not experience any recurrence and progression-free survival was reached at 125, 121, 73 and 21 months, respectively (96). Although basic experiments continue to provide data supporting the efficiency of melatonin in the treatment of leukemia (97), no clinical trials have been undertaken recently.

2.11. Brain Tumors.

Some basic experiments have demonstrated the antiangiogenic and antiproliferative effects of melatonin in neuroblastoma cells (98). The role of melatonin in brain tumors was assayed almost 25 years ago by Lissoni *et al*. (99). Their study included 30 glioblastoma patients, who were assigned, at random, to receive radiotherapy alone or in combination with oral melatonin (20 mg/daily) until disease progression. The survival curves, as well as the survival at one year were significantly higher in patients receiving melatonin with the radiotherapy (99). A more recent study was carried out in patients with brain metastasis treated with radiotherapy (30 Gy, 10 fractions, in the afternoon) who received either melatonin (20 mg at morning or evening, until neurological deterioration or death) or placebo, in order to evaluate the effects of the indoleamine on survival as well as on the time course of neurologic deterioration. The treatment with melatonin did not improve the prognosis of these patients (100).

2.12. Lung cancer.

Non-small-cell lung cancer (NSCLC) is a leading cause of cancer death worldwide and melatonin has been proposed as a potential anticarcinogen for this kind of tumors (101). Melatonin, as part of complex treatments including different drugs, has been assayed for NSCLC. A clinical trial carried out by Lissoni´s group analyzed 100 consecutive patients with metastatic NSCLC who were randomly assigned to receive either chemotherapy (cisplatin and etoposide) alone or associated with melatonin (20 mg/day). Both, tumor regression and 5-year survival rates were significantly higher in those patients treated with melatonin plus chemotherapy (102). Norsa and Martino, conducted two clinical trials with patients suffering from NSCLC. The first enrolled twenty-eight patients with advanced NSCLC (stage IIIB or IV) not previously subjected to chemotherapy or surgery. Patients received a multidrug treatment including somatostatin, vitamin D, retinoids, bromocriptin, cyclophosphamide and melatonin. The authors of this trial concluded that this treatment improves survival (median overall survival was 12.9 months), as well as cough, dyspnea and other symptoms associated

with the malignancy such as pain, sleep troubles, and fatigue (103). In a second trial, carried out this time with NSCLC patients previously treated with chemotherapy, the results obtained with the multi-drug treatment that included melatonin were also similar to those previously obtained in chemotherapy-naive patients (104).

Lissoni studied 148 patients (74 control and 74 experimental) suffering NSCLC and receiving chemotherapy (cisplatin plus either etoposido or gemcitabine) and melatonin 20 mg/day or placebo at random. The survival at two years was significantly higher in patients receiving melatonin concomitantly with chemotherapy (36). In a more recent trial (105), also conducted with people diagnosed whit advanced NSCLC, patients were randomly assigned to a treatment program with 10 or 20 mg/day of melatonin or placebo, in addition to a standard chemotherapy regimen. The authors describe an improvement of health-related quality of life in the patients receiving melatonin, although neither survival nor incidence of adverse effects were significantly modified by adding melatonin to chemotherapy.

3. USEFULNESS OF MELATONIN TO REDUCE THE SIDE EFFECTS OF CANCER TREATMENTS OR TO ALLEVIATE SYMPTOMS OF TUMORAL ILLNESS

Table I summarizes the clinical trials carried out to assess the possible role of melatonin in reducing some of the side effects of chemotherapy or radiotherapeutic treatments used in cancer therapy. The table also includes clinical assays designed to determine whether melatonin reduces some of the symptoms common to different tumor illnesses such as sleep disturbances, asthenia, anorexia, etc., and, in general, all the parameters assessed in each trial that define what it is termed "quality of life".

Table I. Summary of clinical studies about the usefulness of melatonin in alleviating side effects of conventional cancer treatments as well as in reducing the intensity of several symptoms common to tumor illness.

Type of trial & (Ref.)	Side effects studied	Patients	Treatment	Outputs
Phase II, prospective, R, PC, DB. (106)	Radiation-induced dermatitis during radiotherapy for breast cancer.	Women who underwent breast-conserving surgery for stage 0-2 breast cancer.	Mel. emulsion (n = 26) or placebo (n = 21) twice daily during radiation treatment and for 2 weeks after the end of radiotherapy.	Mel. emulsion significantly reduced radiation dermatitis compared to controls.
R, PC, DB. (107)	Delirium and distressing neuropsychi-atric syndrome in palliative care.	60 adult cancer patients under palliative care.	A single daily dose of rapid-release Mel. (3 mg) or placebo, at 21:00 ± 1 h, from day 1 to day 28 of admission.	Clin.Trials. gov: NCT02200172. Study completion data April 2016. Results still not published.
R, PC, DB. (108)	Sleep disturbances.	Women undergoing surgery for breast cancer	Mel. (6 mg, n = 27) or placebo (n = 21) taken approximately 1 h before bedtime 3 nights preoperatively until at least one week after surgery.	Mel. significantly improved the after surgery sleep efficiency and wake after sleep onset, but had no effects on other objective sleep parameters nor in subjective sleep quality.
Prospective phase II trial based	Fatigue and sleep disturbances.	32 woman with metastatic breast cancer,	Mel. (5 mg daily at bedtime) for 2 months.	Melatonin: - Improved objective and subjetive sleep

on repeated measures each patient being his own control. (109)		under hormonal or trastuzumab therapy.		quality, sleep fragmenta-tion and quantity, fatigue severity, quality of life, and social functions. - Did not change circa-dian rhythmicity measu-red by actigraphy. - Did not change the diurnal rhythm of cortisol. - Increased morning expression of clock genes.
R, PC, DB, crossover trial. (110)	Physical fatigue and other symptoms. Quality of life (questionnaire).	72 patients with advanced cancer (stage IV cancer of TNM classification) receiving palliative care.	Mel. (1 week, 20 mg/ day, orally, at night) or placebo. Patients were crossed over receiving the opposite treatment for another week. A two days washout period between both treatments was implemented.	Melatonin was not found to improve fatigue or other symptoms.
R, PC, DB. (105)	Adverse events, quality of life and survival.	Advanced non small cell lung cancer (NSCLC) under chemotherapy.	Mel. (10 mg or 20 mg) or placebo for 2, 3 or 7 months.	Mel. plus chemotherapy: - Did not affect survival and adverse events. - A trend for better heal-th related with quality of life was observed.
R, PC, DB, DD. (22)	Chemoradiation-induced oral mucositis complications in head and neck cancer patients.	39 patients with head and neck cancer under concurrent chemoradi-ation.	Adjuvant Mel. gargle (20 mg) or placebo before irradiation, and Mel. capsules (20 mg) or placebo taken before bedtime during 7 weeks of concurrent chemoradiation.	Treatment with Mel. as an adjuvant delayed the onset of oral mucositis and reduced the amount of morphine for the pain treatment compared to controls.
R, PC, DB. (111)	Depression, anxiety and other parameters of quality of life (fatigue, pain or sleepiness.	54 women, (30-75 years old), undergoing surgery for breast cancer	Mel. (6 mg, orally, n = 28) or placebo (n = 26) for 3 months from 1 week before surgery.	Mel. significantly reduced the risk of depressive symptoms but was not found to improve other symptoms.
R, PC, DB. (112)	Sleep, mood and hot flashes.	Postmenopaus-al breast can-cer survivors (n= 95).	Mel. (3 mg, n = 48) or placebo (n = 47) daily for 4 months.	Mel. improved sleep quality but had no effects on mood nor hot flashes.
R, PC, DB. (113)	Loss of appetite and other symptoms.	48 patients with advanced cancer and cachexia.	Patients received Mel. (20 mg, orally) or placebo before bedtime for 28 days.	There were no significant differences in appetite loss or other side effects that affect the quality of life between the Mel. or placebo groups.

Prospective phase II trial based on repeated measures each patient being his own control. (96)	Relapse and median progression-free survival.	4 relapsed patients with chronic lymphocytic leukemia.	Combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin (oral, 20 mg/day, 10mg at 2 h pm and 10 at 9 h pm), and ACTH.	Partial remission after 2 months. No patients had disease recurrence, and progression-free survival was not yet been reached (125, 121, 73 and 21 months, respectively).
R, DB. (114)	Pelvic irradiation-induced lymphocyto-penia.	20 rectal or uterine cervix cancer patients subjected to radiation for five weeks (total dose 50.4 Gy of radiation.	Mel. alone (20mg/day), Mel and 5-methoxytriptamine (5-MTT) (1mg/day) or subcutaneous low doses of IL-2 (3 MIU/day).	Mel. alone or in combination with 5-MTT did not improve the reduction of the number of lymphocytes, whereas IL-2 increased it.
R, DB. (115)	Tumor progression and survival.	846 patients with untreatable metastatic solid tumors: NSCLC or gastro-intestinal tract tumors).	Palliative care alone or in combination with Mel. (20 mg/day, orally, at bedtime) or with s.c. low-dose IL-2 (3 MIU/day) for 5 days/week during 4 consecutive weeks.	Mel. significantly increased the disease stabilization and survival time in comparison with palliative care alone. The combination of Mel. with IL-2 caused a further improvement on the tumor progression and survival time.
Trial based on repeated measures each patient being his own control. (104)	Survival, clinical status and toxicity.	23 patients with metasta-tic lung adeno-carcinoma and poor perfor-mance status under previous chemotherapy treatment.	Daily, combination of somatostatin, retinoids, Mel. (oral, 20 mg/day, 10mg at 2 h pm and 10 at 9 h pm), vitamin D, bromocriptine and cyclophosphamide.	This multidrug regimen improved disease-related symptoms and was well tolerated.
R. (116)	Association of nocturnal light and risk of cancer by Mel. suppression.	11 healthy young men.	Salivary Mel. levels were measured during 3 nonconsecutive nights over a 2-week period under dim light (< 5 lux), bright light (800 lux) and filtered light (800 lux) at hourly intervals between 2000 and 0800 h.	Preventing Mel. defi-ciencies using lenses that block light of low wavelength represents a cost-effective, practical solution to prevent the increased cancer rates in shift workers.
Phase II, R. (100)	Survival, neurologic deterioration and toxicity or efficacy of Mel.	Patients with brain metastases under radiotherapy.	Mel. (20 mg, given in the morning or at bedtime) in combination with radiation (30 Gy in 10 fractions).	High-dose Mel. had no beneficial effects compared to patients treated with whole-brain radiotherapy.
R. (117)	Serum tryptophan (Trp) and Mel. concentration changes.	72 patients with NSCLC under chemo-therapy treatment (cisplatin + vinorelbine).	Control group: 250 ml/d amino acids parenteral nutritional (PN) Therapy group: 500 ml/d amino acids PN.	Amino acid PN support significantly increased the concentration of serum Mel. and Trp in NSCLC patients receiving chemotherapy

				and this beneficial effect was even greater with the 500 ml/d amino acid PN support treatment.
Trial based on repeated mesures each patient being his own control. (103)	Survival, clinical benefits and toxicity of the multidrug regimen.	28 advanced NSCLC patients with poor performance status.	Daily, combination of retinoids, Mel. (oral, 20 mg/day, 10mg at 2 h pm and 10 at 9 h pm), vitamin D, bromocriptine and cyclophosphamide.	This combination improved the survival as well as the quality of life. In addition there were no side effects.
R, pilot study. (118)	Serum or plasma levels of biochemical variables associated with cachexia (TNFα, IL-1β, soluble IL-2R, IL-6, IL-8; and fatty acids: eicosap-entaenoic, doco-sahexanoid, arachidonic and, linoleic).	24 patients with advanced gastro-intestinal cancer.	Mel. (18 mg/d) and/or fish oil (30 mL/d) daily for 4 weeks.	There were no significant changes on the studied biochemical variables related with cachexia. Nevertheless, this combination could stabilize the weight of this kind of patients.
R, pilot study. (119)	Quality of life, mood, stress and levels of cortisol, dehydroepian-drosterone sulfate and Mel.	Patients with an early stage of breast cancer (n = 59) or prostate cancer (n = 10).	Mindfulness-based stress reduction meditation (MBSR) program daily for 8 weeks.	MSBR improved quality of life, stress symptoms and sleep quality; and it has possibly beneficial changes in hypothalamic-pituitary-adrenal axis. However, there were no significant changes in mood.
Prospective study. (29)	Clinical efficacy of transcatheter arterial chemo-embolization (TACE) and in combination with Mel.	100 inoperable advanced primary hepatocellular cancer patients.	TACE (50 patients) or TACE + Mel. (20 mg/d at 8:00 pm orally, 7 days before TACE) (50 patients).	Mel. could protect liver function from the damage caused by TACE and increased the immunological activities of patients. In addition, Mel. improved the effect of TACE by increasing the survival and resection rates.
R. (102)	Survival and efficacy of chemotherapy when it is combined with Mel.	100 metastatic NSCLC patients under chemotherapy treatment.	All the patients received chemotherapy (cisplatin and etoposide) with or without Mel. (20 mg/d orally, at bedtime) for 5 years.	The survival of patients treated with Mel. was significantly higher. Moreover, chemothera-py was better tolerated in patients who received Mel.

R. (37)	Efficacy of chemotherapy combined with irinotecan (CPT-11) and/or Mel.	30 metastatic colorectal cancer patients previously treated with 5-fluorouracil.	Weekly low-dose of CPT-11 (i.v. at 125 mg/m^2/week for 9 consecutive weeks) alone or in combination with Mel. (20 mg/d, orally, during the nights).	This study shows that Mel. could improve the efficacy of weekly low-dose CPT-11.
R. (120)	Cisplatin-induced anemia during chemotherapy for advanced lung cancer.	20 metastatic lung cancer patients treated with cisplatin and etoposide.	Patients were treated with chemotherapy alone or in combination with 5-methoxytryptamine (5-MTT) (1 mg/d orally, at bedtime).	Anemia was signifi-cantly reduced when chemotherapy was combined with 5-MTT. In addition, the progression of the disease was significantly lower in this group.
Phase II, R. (93)	Toxicity, response to the treatment and progression of the illness.	20 patients with low-grade non-Hodkin's lymphoma (NHL) at advanced stage.	Patients were treated for 1 month with a combi-nation of cyclophospha-mide, somatostatin, bromocriptin, retinoids, Mel (oral, 20 mg/day, 10 mg at 2 h pm and 10 at 9 h pm), and ACTH. This multidrug regimen was continued for 2 addition-al months in patients with stable or responding disease. After 3 months, the responding patients continued the treatment for 3 additional months.	This combination was well tolerated and effective in treatment of this pathology.
R, DB. (121)	Myeloprotective effect of Mel. (hemotological parameters).	20 metastatic lung cancer patients treated with carboplatin and etoposide.	- All the patients recei-ved carboplatin on the first day and etoposide (150 mg m (-2) i.v.) on days 1-3 every 4 weeks. - These patients received Mel. (40 mg/d, orally, at bedtime) or placebo for 21 days, starting 2 days before chemotherapy.	The combination with Mel. did not show protection against the myelotoxic effect of chemotherapy.
Phase II. (122)	Thrombocyto-penia	14 metastatic breast cancer patients with thrombocyto-penia.	Women were treated weekly with low-dose epirubicin (25 mg/m2 i.v.) plus Mel. (20 mg/day, orally, at bedtime, starting 7 days before chemotherapy).	Mel. prevents chemotherapy-induced platelet decrease.
Eleven phase II, in-dependent, multicentre, uncontrolle d	Evaluation of antitumor activity of Di Bella multitherapy treatment. (response and toxicity).	386 patients with metastatic cancer.	- Patients were treated daily with Di Bella multitherapy (Mel, bro-mocriptine, either somatostatin or octreotide, and retinoid.	This multidrug regiment was not sufficiently effective due to no patient showing complete remission.

trials. (123)			- Cyclophosphamide and hydroxyurea were added in some trials).	
R. (124)	Evaluation of the response to the combination with aloe vera; progression of the pathology; survival and toxicity of the treatment.	50 patients suffering untreatable solid carci-nomas (lung cancer, gastro-intestinal tract tumors, breast cancer or brain glioblastoma)	Mel. alone (20 mg/day orally, in the evening) or in combination with aloe vera (1 mL twice/day).	This biotherapeutic combination could have some therapeutic advantages, such as stabilizing of the disease and survival. Apart from this, this natural cancer therapy is well tolerated.
R. (125)	Clinical response and toxicity.	70 metastatic NSCLC patients with poor clinical state under chemotherapy treatment.	All the patients received chemotherapy over 3 days (cisplatin (20 mg/m2/day i.v.) and etoposide (100 mg/m2/day i.v.)) with or without Mel. (20 mg/day orally, at bedtime). Cycles were repeated at 21-day periods.	Not only was the response rate higher in patients treated with Mel. but the survival was also better. Moreover, chemo-therapy was better tolerated in patients who received Mel.
R. (126)	Survival, toxicity and quality of life.	30 brain glioblastoma patients treated with radical or adjuvant radiotherapy.	Radiotherapy alone (60 Gy) or in combination with Mel. (20 mg/day, orally) until disease progression.	This study showed that the combination of radiotherapy combined with Mel. increased survival time. Moreover, the toxicity was lower in patients concomitantly treated with this pineal hormone.

Abbreviations: R=Randomized, PC=Placebo Controlled; DB=Double Blind; DD=Double Dummy; Mel=Melatonin; NSCLC=Non Small Cell Lung Cancer.

4. CONCLUSIONS

It is remarkable that most of the clinical assays on the usefulness of melatonin as an anticancer drug carried out in the last 25 years belong to a single group, Paolo Lissoni *et al*. at the Institute of Biological Medicine of Milan (Italy). Obviously, Lissoni´s group's contribution to this subject is highly valuable. Their studies, however, have some weaknesses, which are probably attributable to the general limitations inherent in clinical research. Thus, their studies were generally conducted with patients suffering from untreatable advanced stage cancers with poor clinical status, that is to say: terminally ill patients. Under these circumstances, it was difficult to obtain positive outcomes. Furthermore, patients were frequently grouped under the term "advanced solid tumors" including those patients with tumors of the breast, lung, gastrointestinal tract as well as brain glioblastomas, etc., who were, in each case, subjected to different first-line treatments. Finally, several of the outcomes analyzed, such as partial remission, or disease stabilization, are difficult to quantify for statistical analysis. These facts must be taken into consideration when evaluating the results obtained with the treatments with melatonin. Perhaps the major contribution of Lissoni´s group was to recognize the relevance of the immune system in the fight against cancer by associating IL-2 with melatonin, which has been considered as an immunoenhancer. The results of Lissoni´s trials also have in

common their assessment of the low toxicity of melatonin and its value in reducing the side effects of conventional anticancer therapies.

At present, 40 clinical trials focusing on melatonin and cancer are listed in the ClinicalTrials.gov database, and only half of these have already been completed. Seventeen of these studies explore the influence of melatonin treatments on the quality of life of cancer patients under different chemotherapy or radiotherapy protocols. Parameters such as appetite, asthenia, cachexia, fatigue, sleep disturbances, circadian disturbances, pain, anxiety, delirium, depression and cognitive impairment are evaluated in these patients. Seven trials studied the effectiveness of melatonin as an adjuvant to other treatments (vitamin D, metformin, etc.) to influence the evolution of tumor processes. Five studies evaluated the usefulness of melatonin to reduce the side effects (mucositis, dermatitis, etc.) of conventional anticancer treatments. One clinical trial was designed to establish the maximum tolerated daily dose of melatonin in children with relapsed solid tumors. In the remaining clinical trials, melatonin was not exogenously administered but its plasmatic concentration was measured as a possible mediator of the influence of either the carcinogenic effects of different environmental factors, or the tumor response to non-pharmacologic therapies. These trials include: a) shift work as a risk factor of BC; b) the effects of environmental lighting and light therapies on the evolution of several tumors; c) circadian disruption and cancer progression; the role of exercise, meditation, musical therapy, yoga, etc. in improving the quality of life of cancer patients.

The conclusions we have obtained from this review are the following:

1. The disparity between the high number of basic studies with promising results highlighting the possible role of melatonin as an anticancer drug from *in vitro* and *in vivo* studies, and the extremely low number of clinical trials to check its value, should give us pause to think about the causes. Perhaps the consideration of melatonin in many countries as a "food supplement" with not necessarily medical connotations or associations, has trivialized its use and thereby exerted a negative influence on its consideration for use in cancer treatments. Another reason may be that oncologist are now mainly looking for therapies based on immunology, or the development of drugs which act on highly specific molecular targets.

2. Medical interest in the use of melatonin alone as a first line treatment for cancer appears to have been discarded.

3. Melatonin is an extremely interesting adjuvant to practically any conventional cancer therapy. The improvements it offers to the quality of life of patients, by normalizing sleep and alleviating general symptoms associated with tumor disease and treatments, justify and recommend its use.

4. Regarding the particular case of hormone-dependent BC, melatonin deserves especial consideration. The antiestrogenic properties of melatonin acting simultaneously as both a SERM and a SEEM gives to this indoleamine unique features for its use in association with other synthetic molecules by increasing their efficacy. Furthermore, melatonin reduces the side effects of synthetic SERMs and SEEMs.

5. Among the different risk factors for BC, increased estrogenic stimulation of mammary tissue appears as a common cause (HRT, exposure to xenoestrogens, adipose tissue as sources of excessive estrogens, etc.). In these cases, melatonin, with its low toxicity (appropriate for extended duration treatments) and its SERM and SEEM properties, proves to be an ideal preventive treatment to reduce BC in populations with elevated risk. The authors of this review strongly recommended clinical assays to demonstrate the usefulness of melatonin for this purpose.

From these conclusions we recommend focusing the future clinical studies in two directions: a) the evaluation of the usefulness of melatonin in breast cancer prevention in groups with an elevated risk for this malignancy and, b) to establish the use of melatonin as an

adjuvant therapy to alleviate the general symptoms associated with tumors as well as the side-effects of various anticancer treatments.

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AUTHORSHIPS

AGG contributed with the confection of Table I. NRR was in charge of compiling the bibliography. EJSB was responsible for the conception and redaction of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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