**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 | Side effects studied | Patients | Treatment | Outputs | Ref. |
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| Phase II, prospective, randomized, placebo-controlled double-blind study. | Radiation-induced dermatitis during radiotherapy for breast cancer. | Women who underwent breast-conserving surgery for stage 0-2 breast cancer. | Melatonin emulsion (n = 26) or placebo (n = 21) for taken twice daily during radiation treatment and for 2 weeks after the end of radiotherapy. | Treatment with melatonin-containing emulsion significantly reduced radiation dermatitis compared to controls. | 106 |
| Randomized, placebo-controlled, double-blind trial. | Delirium and distressing neuro-psychiatric syndrome in palliative care. | 60 adult cancer patients under palliative care. | A single daily dose of rapid-release melatonin (3 mg) or placebo, at 21:00 ± 1 h, from day 1 to day 28 of admission. | ClinicalTrials.gov: NCT02200172 Study completion data April 2016. Results still not published. | 107 |
| Double-blind, placebo-controlled, randomized clinical trial. | Sleep disturbances. | Women undergoing surgery for breast cancer | Melatonin (6 mg, n = 27) or placebo (n = 21) taken approximately 1 hour before bedtime 3 nights preoperatively until at least one week after surgery. | Melatonin 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. | 108 |
| Prospective phase II trial based on repeated measures each patient being his own control. | Fatigue and sleep disturbances. | 32 woman with metastatic breast cancer, under hormonal or trastuzumab therapy. | Melatonin (5 mg daily at bedtime) for 2 months. | Melatonin:<br>- Improved objective and subjetive sleep quality, sleep fragmentation and quantity, fatigue severity, quality of life, and social functions.<br>- Did not change circadian rhythmicity measured by actigraphy.<br>- Did not change the diurnal rhythm of cortisol.<br>- Increased morning expression of clock genes. | 109 |
| Double-blind, randomized, placebo-controlled crossover trial. | Physical fatigue and other symptoms. Quality of life (questionnaire). | 72 patients with advanced cancer (stage IV cancer of TNM classification) receiving palliative care. | Melatonin (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. | 110 |

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| Randomized, double-blind, placebo-controlled trial. | Adverse events, quality of life and survival. | Patients with advanced non-small cell lung cancer under chemotherapy. | Melatonin (10 mg or 20 mg) or placebo for 2, 3 or 7 months. | Melatonin in combination with chemotherapy:<br>- Did not affect survival and adverse events.<br>- A trend for better health related with quality of life was observed. | 105 |
| Randomized, double-blind, double dummy, placebo-controlled clinical trial. | Chemoradiation-induced oral mucositis complications in head and neck cancer patients. | 39 patients with head and neck cancer under concurrent chemoradi-ation. | Adjuvant melatonin gargle (20 mg) or placebo before irradiation, and melatonin capsules (20 mg) or placebo taken before bedtime during 7 weeks of concurrent chemoradiation. | Treatment with melatonin as an adjuvant delayed the onset of oral mucositis and reduced the amount of morphine for the pain treatment compared to controls. | 22 |
| Randomized, double-blind, placebo-controlled trial | Depression, anxiety and other paramet-ers of quality of life (fatigue, pain or sleepiness. | 54 women, 30-75 years, undergoing surgery for breast cancer | Melatonin (6 mg, orally, n = 28) or placebo (n = 26) for 3 months from 1 week before surgery. | Melatonin significantly reduced the risk of depressive symptoms but was not found to improve other symptoms. | 111 |
| Randomized, double-blind, placebo-controlled trial. | Sleep, mood and hot flashes. | 95 postmenopausal breast cancer survivors. | Melatonin (3 mg, n = 48) or placebo (n = 47) daily for 4 months. | Melatonin improved sleep quality but had no effects on mood nor hot flashes. | 112 |
| Randomized, double-blind, placebo-controlled trial. | Loss of appetite and other symptoms. | 48 patients with advanced cancer and cachexia. | Patients received melatonin (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 melatonin or placebo groups. | 113 |
| Prospective phase II trial based on repea-ted mesures each pa-tient being his own control. | Relapse and median progression-free survival. | 4 relapsed patients with chronic lymphocytic leukemia. | Combination of cyclophospha-mide, somatostatin, bromocriptine, retinoids, melatonin 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). | 96 |
| Randomized trial. | Pelvic irradiation-induced lymphocytopenia. | 20 rectal or uterine cervix cancer patients subjected to radiation for five weeks (total dose 50.4 Gy of radiation.. | Melatonin alone (20mg/day), melatonin and 5-methoxytripto-mine (5-MTT) (1mg/day) or subcutaneous (s.c.) low doses of IL-2 (3 MIU/day). | Melatonin alone or in combination with 5-MTT did not improve the reduction of the number of lymphocytes; whereas Il-2 increased it. | 114 |

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| Randomized trial. | Tumor progression and survival. | 846 patients with untreatable metastatic solid tumors (non-small cell lung cancer or gastrointestinal tract tumors). | Palliative care alone or in combination with melatonin (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. | Melatonin significantly increased the disease stabilization and survival time in comparison with palliative care alone. The combination of melatonin with IL-2 caused a further improvement on the tumor progression and survival time. | 115 |
| Trial based on repeated measures each patient being his own control. | Survival, clinical status and toxicity. | 23 patients with metas-tatic lung adenocarcino-ma and poor performan-ce status under previous chemotherapy treatment. | Daily, combination of somatostatin, retinoids, melatonin, vitamin D, bromocriptine and cyclophosphamide. | This multidrug regimen improved disease-related symptoms and was well tolerated. | 104 |
| Not indicated | Association of nocturnal light and risk of cancer by melatonin suppression. | 11 healthy young men. | Salivary melatonin levels were measured during 3 noncon-secutive 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 melatonin deficiencies using lenses that block light of low wavelength represents a cost-effective, practical solution to prevent the increased cancer rates in shift workers. | 116 |
| Randomized, phase II trial. | Survival, neurologic deterioration and toxicity or efficacy of melatonin. | Patients with brain metastases under radiotherapy. | Melatonin (20 mg, given in the morning or at bedtime) in combination with radiation (30 Gy in 10 fractions). | High-dose melatonin had no beneficial effects compared to patients treated with whole-brain radiotherapy. | 100 |
| Randomized trial. | Serum tryptophan (Trp) and melatonin (MT) concentration changes. | 72 lung cancer patients (NSCLC) under chemotherapy 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 MT and Trp in NSCLC patients receiving chemotherapy and this beneficial effect was even greater with the 500 ml/d amino acid PN support treatment. | 117 |
| Trial based on repeated mesures each patient being his own control. | Survival, clinical benefits and toxicity of the multidrug regimen. | 28 advanced non-small-cell lung cancer patients (NSCLC) with poor performance status . | Daily, combination of retinoids, melatonin, vitamin D, bromocriptine and cyclophosphamide. | This combination improved the survival as well as the quality of life. In addition there were no side effects. | 103 |

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| Randomized pilot study. | Serum or plasma levels of biochemical variables associated with cachexia (TNFα, IL-1β, soluble IL-2R,IL-6, and IL-8; and the fatty acids: eicosapentaenoic, docosahexanoid acid, arachidonic acid, linoleic acid. | 24 patients with advanced gastrointestinal cancer. | Melatonin (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. | 118 |
| Randomized pilot study. | Quality of life, mood, stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin. | 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 (HPA) axis functioning. However there were no significant changes in mood. | 119 |
| Prospective study. | Clinical efficacy of transcatheter arterial chemoembolization (TACE) and in combination with melatonin. | 100 inoperable advanced primary hepatocellular cancer patients. | TACE (50) or with melatonin (20 mg/d at 8:00 pm orally, 7 days before TACE (50)). | Melatonin could protect liver function from the damage caused by TACE and increased the immunological activities of patients. In addition, this indolamine improved the effect of TACE by increasing the survival and resection rates. | 29 |
| Randomized trial. | Survival and efficacy of chemotherapy when it is combined with melatonin. | 100 metastatic NSCLC patients under chemotherapy treatment. | All the patients received chemotherapy (cisplatin and etoposide) with or without melatonin (20 mg/d orally, at bedtime) for 5 years. | The survival of patients treated with melatonin was significantly higher. Moreover, chemotherapy was better tolerated in patients who received melatonin. | 102 |
| Randomized study. | Efficacy of chemotherapy combined with irinotecan (CPT-11) and/or melatonin. | 30 metastatic colorectal cancer patients previously treated with 5-fluorouracil. | Weekly low-dose of CPT-11 (i.v. at 125 mg/m2/week for 9 consecutive weeks) alone or in combination with melatonin (20 mg/d, orally, during the nights). | This study shows that melatonin could improve the efficacy of weekly low-dose CPT-11. | 37 |

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| Randomized trial. | 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 significantly reduced when it chemotherapy was combined with 5-MTT. In addition, the progression of the disease was significantly lower in this group. | 120 |
| Phase II trial. | 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 combination of cyclophosphamide, somatosta-tin, bromocriptin, retinoids, melatonin and ACTH. This multidrug regimen was contin-ued for 2 additional months in patients with stable or respon-ding 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. | 93 |
| Double-blind, randomized trial. | Myeloprotective effect of melatonin (haemotological parameters). | 20 metastatic lung cancer patients treated with carboplatin and etoposide. | - All the patients received carboplatin on the first day and etoposide (150 mg m(-2) i.v.) on days 1-3 every 4 weeks.<br>- These patients received melatonin (40 mg/d, orally, at bedtime) or placebo for 21 days, starting 2 days before chemotherapy. | The combination with melatonin did not show protection against the myelotoxic effect of chemotherapy. | 121 |
| Phase II study. | Thrombocytopenia | 14 metastatic breast cancer patients with thrombocytopenia. | Women were treated weekly with low-dose epirubicin (25 mg/m2 i.v.) plus melatonin (20 mg/day, orally, at bedtime, starting 7 days before chemotherapy). | Melatonin prevents chemotherapy-induced platelet decrease. | 122 |

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| Independent, multicentre, uncontrolled, phase II trials. | 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 (melatonin, bromocriptine, either somatostatin or octreotide, and retinoid.<br>- Cyclophosphamide and hydroxyurea were added in some trials). | This multidrug regiment was not sufficiently effective due to no patient showing complete remission. | 123 |
| Randomized study. | 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 carcinomas (lung cancer, gastrointestinal tract tumors, breast cancer or brain glioblastoma) | Melatonin 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. | 124 |
| Randomized study. | 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 melatonin (20 mg/day orally, at bedtime). Cycles were repeated at 21-day periods. | Not only was the response rate higher in patients treated with melatonin but the survival was also better. Moreover, chemotherapy was better tolerated in patients who received melatonin. | 125 |
| Randomized trial. | Survival, toxicity and quality of life. | 30 brain glioblastomas patients treated with radical or adjuvant radiotherapy. | Radiotherapy alone (60 Gy) or in combination with melatonin (20 mg/day, orally) until disease progression. | This study showed that the combination of radiotherapy combined with melatonin increased survival time. Moreover, the toxicity was lower in patients concomitantly treated with this pineal hormone. | 126 |