High Dose Melatonin Therapy - An Ideal Adjuvant Anti-cancer Therapy

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Melatonin Facts

- Produced and released in pineal gland in darkness. Immediately suppressed by all light but red light.
- Not a soporific. You can take it during the day, as well as at bedtime, without any adverse effect.
- Side effects: no serious side effects. Some patients report sleep disturbances and AM sleepiness.
- Dr. Pierpaoli, one of the world's leading melatonin researchers, has successfully used daily dosages ranging from 0.1 to 200 mg. That's a 2,000-fold difference between the lowest dose and the highest! Studies on mice show that even at astronomical doses of 300 mg per day for two years, there were no side effects.

Melatonin Facts

- Testing for melatonin – AM urine for 6-sulfatoxy melatonin. ZRT Laboratory. Ph 866-600-1636 Fax: 503-466-1636 | info@zrtlab.com
- Peak plasma level after PO ingestion is about 1 hour. Levels sustained for 3-4 hours.
- Rapidly enters the central nervous system and crosses the blood-brain barrier.
- Exogenous melatonin does not alter the levels of any other hormones
- No negative feedback inhibition

Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis.

Mills, E., P. Wu, et al. *J Pineal Res*. 2005 November;39(4):360-6.

- Melatonin activates anti-neoplastic immune reactivity
- Direct anticancer action
- Protects against chemo radiation damage
- On average, the combined results of these studies showed that melatonin reduced the risk of dying by 44%.
- The effects were consistent no matter what dose they used.
- None of the patients had any significant side effect from the melatonin.
- "The substantial reduction in risk of death, low adverse events reported, and low costs related to this intervention suggest great potential for melatonin in treating cancer."

Basic mechanisms involved in the anti-cancer effects of melatonin.

Mediavilla MD[1], Sanchez-Barcelo EJ, et al. Curr Med Chem 2010;17(36):4462-81.

- "Melatonin has oncostatic properties in a wide variety of tumors."
- Mitochondrial stimulant.
- Regulation of estrogen receptor expression and transactivation.
- Modulation of the enzymes involved in the local synthesis of estrogens.
- Modulation of cell cycle and induction of apoptosis.
- Inhibition of telomerase activity
- Inhibition of metastasis

Basic mechanisms involved in the anti-cancer effects of melatonin.

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- Direct anti-neoplastic effects.
- Decreases cell proliferation at low concentrations.
- Direct cytotoxic effect occurs with high concentrations
- Stimulation of cell differentiation
- Induction of apoptosis
- Anti-angiogenesis
- A synergistic effect has been found in several cancer types when it is administered in combination with chemotherapy.

Cancer metastasis: Mechanisms of inhibition by melatonin.

Su SC, Hsieh MJ, Yang WE, J Pineal Res. 2017 Jan;62(1).

- "Due to the broad range of melatonin's actions, the mechanisms underlying its ability to interfere with metastases are numerous. These include modulation of cell-cell and cell-matrix interaction, extracellular matrix remodeling by matrix metalloproteinases, cytoskeleton reorganization, epithelial-mesenchymal transition, and angiogenesis."
- "The evidence discussed herein will serve as a solid foundation for urging basic and clinical studies on the use of melatonin to understand and control metastatic diseases."

Melatonin uptake through glucose transporters: a new target for melatonin inhibition of cancer.

Hevia D, González-Menéndez P, J Pineal Res. 2015 Mar;58(2):234-50.

- "Some functions of melatonin are mediated by its membrane receptors but others are receptor-independent. For the latter, melatonin must enter into the cell."
- "Herein, it is demonstrated that members of the SLC2/GLUT family glucose transporters have a central role in melatonin uptake."
- "Glucose concentration and the presence of competitive ligands of GLUT1 affect the concentration of melatonin into cells."
- "As a regulatory mechanism, melatonin reduces the uptake of glucose and modifies the expression of GLUT1 transporter in prostate cancer cells. More importantly, glucose supplementation promotes prostate cancer progression in TRAMP mice, while melatonin attenuated glucose-induced tumor progression and prolonged the lifespan of tumor-bearing mice."

Melatonin reduces endothelin-1 expression and secretion in colon cancer cells through the inactivation of FoxO-1 and NF-κβ.

León J, Casado J, et al. J Pineal Res. 2014 May;56(4):415-26.

- "Endothelin-1 (ET-1) is a peptide that acts as a survival factor in colon cancer, inducing cell proliferation, protecting carcinoma cells from apoptosis, and promoting angiogenesis."
- "The data presented show that melatonin inhibits edn-1 mRNA expression, the first step in ET-1 synthesis."
- "In conclusion, melatonin may be useful in treating colon carcinoma in which the activation of ET-1 plays a role in tumour growth and progression."

Melatonin as a potential anticarcinogen for non-small-cell lung cancer.

Ma Z, Yang Y, Fan C· Oncotarget. 2016 Jul 19;7(29):46768-46784

- "Melatonin exerts pleiotropic anticancer effects against a variety of cancer types."
- "Herein, we review the correlation between the disruption of the melatonin rhythm and NSCLC incidence."
- "We also evaluate the evidence related to the effects of melatonin in inhibiting lung carcinogenesis. Special focus is placed on the oncostatic effects of melatonin, including anti-proliferation, induction of apoptosis, inhibition of invasion and metastasis, and enhancement of immunomodulation."
- "We suggest the drug synergy of melatonin with radio- or chemotherapy for NSCLC could prove to be useful."

Melatonin as a treatment for gastrointestinal cancer: a review.

Xin Z, Jiang S, Jiang P. J Pineal Res. 2015 May;58(4):375-87.

- "The ability of melatonin to inhibit gastrointestinal cancer is substantial."
- "In this review, we first clarify the relationship between the disruption of the melatonin rhythm and gastrointestinal cancer."
- "The mechanisms through which melatonin exerts its anti-gastrointestinal cancer actions are explained, including inhibition of proliferation, invasion, metastasis, and angiogenesis, and promotion of apoptosis and cancer immunity."
- "We discuss the drug synergy effects and the role of melatonin receptors involved in the growth-inhibitory effects on gastrointestinal cancer.
- "The information compiled here serves as a comprehensive reference for the anti-gastrointestinal cancer actions of melatonin that have been identified to date."

Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation.

Sanchez-Barcelo EJ, Mediavilla MD, Expert Opin Investig Drugs. 2012 Jun;21(6):819-31.

- "Because of its SERM (selective estrogen receptor modulators) and SEEM (selective estrogen enzyme modulators) properties, and its virtual absence of contraindications, melatonin could be an excellent adjuvant with the drugs currently used for breast cancer prevention (antiestrogens and antiaromatases)."
- "The antioxidant actions also make melatonin a suitable treatment to reduce oxidative stress associated with chemotherapy, especially with anthracyclines, and radiotherapy."
- Melatonin's anti-estrogenic properties are especially useful for breast cancer prevention in cases of obesity, steroid hormone treatment or chronodisruption by exposure to light at night.

Protective and sensitive effects of melatonin combined with adriamycin on ER+ (estrogen receptor) breast cancer.

Ma C, Li LX, Zhang Y, Xiang C, Eur J Gynaecol Oncol. 2015;36(2):197-202.

- ER+ breast cancer rat model was established and then rats were randomly divided into five different groups as follows: control group, Diss group, adriamycin (ADM) group, MLT group, and MLT combined with adriamycin (M+A) group.
- Tumor weights were significantly lighter in M+A group than those in ADM group ($p < 0.05$). Under optical and electro-microscopy, tumor cell apoptosis was obviously increased in MLT group, and tumor cell injury was more severe in M+A group than that in ADM group.
- Decreased E-cadherin expression in cancer cells increases proliferation, invasion, and/or metastasis. Expression of E-cadherin was higher in MLT group and M+A group than that in other groups.
- MLT group had the highest one month survival rate (100%), there was the poorest life quality in ADM group, but the best life quality in MLT.
- "MLT could enhance the sensitivity of tumor to ADM in vivo and improve patient's life quality."

Physiological and pharmacological concentrations of melatonin protect against cisplatin-induced acute renal injury.

J. Pineal Res. 2002 Oct;33(3):161-6.

- Acute tubular necrosis is a major side effect of cisplatin
- "Melatonin is a direct free radical scavenger and indirect antioxidant."
- "We investigated the effects of melatonin on cisplatin-induced changes of renal malondialdehyde (MDA), a lipid peroxidation product, and blood urea nitrogen (BUN) and serum creatine (Cr). The morphological changes in kidney were also examined using light microscopy."
- Melatonin administration either before or after CDDP injection caused significant decreases in MDA.
- The morphological damage to the kidney induced by cisplatin was reversed by melatonin.
- "The results show that pharmacological and physiological concentrations of melatonin reduce cisplatin-induced renal injury."

Melatonin as a radioprotective agent: a review.

Vijayalaxmi, Reiter RJ, et al. Int J Radiat Oncol Biol Phys. 2004 Jul 1;59(3):639-53.

- Melatonin is both a direct and indirect free radical scavenger.
- The radical scavenging ability of melatonin works via electron donation to detoxify hydroxyl radical.
- Ionizing radiation results in the production of hydroxyl radical.
- "The results from many in vitro and in vivo investigations have confirmed that melatonin protects mammalian cells from the toxic effects of ionizing radiation."
- Furthermore, several clinical reports indicate that melatonin administration, either alone or in combination with traditional radiotherapy, results in a favorable efficacy:toxicity ratio during the treatment of human cancers.

Melatonin for Prevention of Breast Radiation Dermatitis: A Phase II, Prospective, Double-Blind Randomized Trial.

Ben-David MA, Elkayam R, et al. Isr Med Assoc J. 2016 Mar-Apr;18(3-4):188-92.

- Radiation-induced dermatitis is commonly seen during radiotherapy for breast cancer.
- randomized, placebo-controlled double-blind study, patients randomly allocated to topical cream twice daily use during radiation treatment and 2 weeks following the end of radiotherapy.
- Grade 1-2 acute radiation dermatitis was 59% vs. 90% in the melatonin group.
- "Patients treated with melatonin-containing emulsion experienced significantly reduced radiation dermatitis compared to patients receiving placebo."

Dosing

- Only red lights in the bedroom.
- Prevention: 180 mg about 30 minutes before bedtime.
- Treatment: 60 mg 3-6x/day
- 300mg two hours before PET/CT
- Melatonin Max – 60 mg pure capsules (www.scientifichealthsolutions.com)
- Melatonin powder – www.purebulk.com
- Zero contraindications