Letter to Editor

Injectable melatonin: an anti-cancer and anti-viral treatment option

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We read with much interest the review by Reiter *et al.* (1) which focused on the hypothesis that inhibition of mitochondrial pyruvate dehydrogenase kinase could explain the role of melatonin in regulating glucose metabolism in cancer cells in view that many cancer cells use cytosolic glycolysis (the Warburg effect). As a consequence, melatonin causes cancer cells to overcome cytosolic glycolysis, reduce tumor biomass and reverse insensitivity to chemotherapy.

Melatonin, or N-acetyl-5-methoxytryptamine, is an indoleamine synthesized from tryptophan by the pineal gland and perhaps all organs, since its production has been found to be associated with mitochondria (2). Notably, high melatonin levels have been suggested to play positive and important roles in health and aging (3), while the deregulation or misalignment of the circadian system and of melatonin circulating levels (4) is associated with negative impacts as epigenetic abnormalities and also with an increased incidence of metabolic, cardiovascular, neurologic and oncologic diseases (4). It is well established that melatonin possesses antioxidant and anti-inflammatory activities, and it influences the sleep–wake cycle, reproduction, and metabolism (5). Melatonin's antioxidant activity is due not only to its ability to act as a scavenger agent but also to its capacity to upregulate antioxidant enzyme activity and downregulate prooxidant enzymes (3).

While melatonin physiological concentration in biological liquids oscillates between 10^{-10} and 10^{-11} M range, a concentration of about 10^{-5} M is required to elicit significant pharmacological effects (6). Moreover, melatonin interacts in a one-to-one ratio with malondialdehyde (MDA) and these findings suggest that melatonin may detoxify unsaturated carbonyls and protect against cellular damage induced by reactive oxidative species (ROS) (7), thus justifying the need of a more generous supplementation of exogenous melatonin in life-threatening pathologies.

Interestingly, in the last decades, various studies investigated the effects of melatonin against cancer and identified its antiproliferative, cytostatic, antioxidant, cytotoxic, proapoptotic, and differentiative activities together with its ability to regulate epigenetic responses (8), which were punctually focused in two publications (9, 10). Other studies have shown as well that melatonin adjunctive co-administration improves the sensitivity of cancers to inhibitory effects of conventional oncologic drugs. More importantly melatonin modifies cancers previously totally resistant to treatment sensitive to the same therapies. More recently the hypothesis that melatonin regulates glucose metabolism further supports the evidence that melatonin reduces tumour biomass and reverses insensitivity of cancer cells to chemotherapy (1). Melatonin further inhibits molecular processes associated with metastasis by limiting the migration of cancer cells into the vascular system and preventing them from establishing secondary growths at distant sites. Moreover, a mounting number of publications are report that melatonin in association with chemotherapy and radiotherapy inhibits the process of resistance, mainly due to the inhibitory influence on VEGF/HIF-1α pathway expression. Progression of cancer is characterized by the stimulation of pro-angiogenic factors, including hypoxia, vascular endothelial growth factor (VEGF), cytokine interleukin-6 and metalloproteinases, in the growing endothelial cells (9). VEGF has been demonstrated to be one of

the most important angiogenesis growth factors that induces permeability, proliferation, migration and tube formation (10). Numerous stimuli, including hypoxia, cytokines and oxidative stress, increase VEGF expression (11). The inhibition of neoangiogenesis is considered to be also an important potential strategy for efficient and effective antitumor agents (including melatonin) that prevent cancer proliferation and metastasis (12).

Kasi R *et al*. (13) further reported that melatonin suppresses proliferation of cancer cells. The study evidenced that co-administration of melatonin in cervical cancer HeLa, in colorectal HT-29 and acute T-cell leukemia (JURKAT) cell lines induces cytotoxicity and apoptosis in a dose-dependent manner, thus underpinning the importance to test *in vivo* high dose-pharmacological levels of melatonin. It is evident that intravenous infusion of high doses of melatonin would represent the most eligible route to treat conveniently patients hospitalized in critical care units or with undergoing oncologic therapies, wherein adequate, accurate and constant dosages and high levels of melatonin would be required.

Hence, the aim of this Letter to Editor is to notify the melatonin community of researchers and clinicians that ultimately, after several attempts, a stable concentrate bulk solution of 10% melatonin (Survivis®) has been successfully achieved. This versatile and ready to use concentrate has to be simply diluted in saline at the desired time and the needed concentration before its use. The industrial bulk solution of 10% melatonin (w/v) has further shown a satisfactory stability profile without the use of preserving agents. Stability studies have been carried out at accelerated conditions (40 ± 2 °C / R.H. 75 ± 5% for 6 months), at long-term conditions (25 ± 2 °C / R.H. 60 ± 5% for 12 months) and also at cryogenic shock conditions (T = -l0 ± 2 °C / R.H. 75 ± 5% for 3 days), using a climatic monitorage storage. In all cases the industrial bulk solution of 10% melatonin has shown a good stability, evidencing only a decrease (about 1%) of the melatonin assay value at the end of the considered period, but always widely within the specifications range. More importantly, the composition is also adequately stable after dilution with saline at room temperature (25 ± 2 °C). The high concentration of melatonin of the novel bulk solution further substantially reduces the ratio volume of ethanol/mg of dissolved melatonin to be administered to patients to treat the oncologic pathologies.

The new concentrate would further avoid the use of dimethylsulfoxide (DMSO) to dissolve parenteral melatonin for preclinical animal studies. DMSO presents high risk of biological interefences and contamination with the results of the search, and is further contraindicated in humans precluding its uniform translation to the clinics.

Despite Survivis® has patent protection in USA (US Pat. 10,342,779) and in Europe (EP application 15778670.8 has been imminently granted), in view that many patients who could promptly benefit of the association melatonin and chemotherapeutic drugs, like sorafenib in hepatocellular carcinoma (HCC) and vemurafenib in melanoma, or as palliative therapy as well for pain control in advanced cancer (14) special licensing authorizations of using concentrate 10% melatonin could be shared upon request from melatonin scientists and clinicians. Similarly, the concentrate 10% melatonin could represent a valuable alternative also for preclinical studies in animal models, wherein until now DMSO has been generally used.

The diluted solution can also be advantageously administered intravenously to humans whenever a therapeutic effective dose of melatonin is required as adjuvant in life threatening conditions such as those caused from Ebola hemorrhagic fever (EHF) (15-17) and Dengue hemorrhagic fever (DHF) or other virus-related diseases. Boga *et al.* (18) reviewed the use of melatonin to treat several viral infections, due to its properties as a potent antioxidant and antioxidant enzyme inducer, a regulator of apoptosis and elicit immune functions. Consequently Survivis® can be administrated to produce high plasmatic levels of melatonin that expectedly could correct bleeding problems, promote platelets and red blood cells production (19), enhance a general protective effect on the nano and capillary system, reduce ecchymosis, petechiae and generalized rush, significantly inhibit the production and reduce the accumulation of proinflammatory cytokines with a remarkable benefit for the involved tissues, in

such critical health conditions.

In summary, Survivis® would definitely represent the preferred administration product for high dose melatonin to critically ill patients, while the second aim of this letter is to coooperate and support melatonin research and clinicians to make available Survivis® vials for a joint participation to more ambitious oncologic research projects focused on high dose parenteral melatonin in combination with other conventional chemotherapeutic agents or radiotherapy applications, with parallel humanitarian and palliative improvements of patient care at the late stage of cancer treatments.

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AUTHORSHIP

EP wrote the first draft of the manuscript and patent information; PV wrote the cancer combined chemotherapeutic treatment and anti-viral treatment and revised the manuscript

CONFLICT OF INTEREST

The authors are managing and regulatory affairs directors of Worphmed Srl.

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