Melatonin: does it have utility in the treatment of haematological neoplasms?

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Melatonin, discovered in 1958 in the bovine pineal tissue, is an indoleamine that modulates circadian rhythms and has a wide variety of other functions. Haematological neoplasms are the leading cause of death in children and adolescents throughout the world. Research has demonstrated that melatonin is a low-toxicity protective molecule against experimental haematological neoplasms, but the mechanisms remain poorly defined. Here, we provide an introduction to haematological neoplasms and melatonin, especially as they relate to the actions of melatonin on haematological carcinogenesis. Secondly, we summarize what is known about the mechanisms of action of melatonin in the haematological system, including its pro-apoptotic, pro-oxidative, anti-proliferative and immunomodulatory actions. Thirdly, we discuss the advantages of melatonin in combination with other drugs against haematological malignancy, as well as its other benefits on the haematological system. Finally, we summarize the findings that are contrary to the suppressive effects of melatonin on cancers of haematological origin. We hope that this information will be helpful in the design of studies related to the therapeutic efficacy of melatonin in haematological neoplasms.

Abbreviations
ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; auto-SCT, autologous stem cell transplantation; CLL, chronic lymphocytic leukaemia; DR, death receptor; NHL, non-Hodgkin lymphoma; NK, natural killer; Th1, T-helper 1
Introduction

According to the Global Cancer Statistics from the American Cancer Society, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide. Among all tumours, haematological neoplasms are the leading cause of death in children and adolescents throughout the world (Torre et al., 2015). Haematological neoplasms, also known as haematological malignancies, are tumours that originate from the blood and blood-forming system (marrow and lymphatic tissue), including leukaemias, lymphomas and multiple myelomas. Most haematological neoplasms are malignant and derive from the abnormal growth of myeloid/lymphoid cell lines. Chemotherapy is an effective method for treating haematological malignancies, especially leukaemia. Initially, we introduce the basic background information on haematological neoplasms and melatonin, as well as melatonin’s suppressive actions on haematological tumours. Secondly, we summarize the antineoplastic mechanisms of melatonin in haematological cancers and drug synergy of melatonin, concomitant with its detoxification of anti-haematological malignancy drugs. Thirdly, other benefits of melatonin on the haematological system are summarized along with contrary opinions, potential direction for further research, as based on the current information and experience. This review highlights recent advances and provides a thorough evaluation of melatonin’s oncostatic potential. This information will hopefully benefit the design of studies for the clinical use of melatonin against haematological neoplasms.

Melatonin and haematological carcinogenesis

Melatonin is a pivotal component of the body’s internal time-keeping system that is associated with human health (Bonmati-Carrion et al., 2014; Hernandez-Resendiz and Zazueta, 2014; Reiter et al., 2014b; Vriend and Reiter, 2015). A conventional definition of carcinogenesis is that it is a pathological alteration of normal cells in response to stimulation by carcinogenic factors, such as chemicals, radiation and microorganisms (Vineis et al., 2010). As mentioned above, numerous studies have shown that melatonin inhibits carcinogenesis in both human and animals (Tanaka et al., 2009; Sanchez-Barcelo et al., 2010). Epidemiological surveys show that melatonin disruption may increase the risk of haematological neoplasms, which is consistent with reduced levels of melatonin in patients with these tumours (Kana et al., 2014b). The so-called melatonin hypothesis proposed that decreased nocturnal production of melatonin may explain the increased risk of cancer in some patients. Disruption of the circadian clockwork is one of the factors that predispose
individuals to haematological neoplasms. Moreover, nocturnal work (night shifts) might disturb the normal secretion of melatonin and elevate the risk of myeloid tumours and lymphoma (Lahti et al., 2008; Yong et al., 2014; Costas et al., 2016). Further research suggests that night shift work might elevate cancer risk by suppressing melatonin secretion (Stevens and Davis, 1996; Reiter et al., 2006). In relation to haematological cancer, Garbazza et al. (2016) reported a case of a 40-year-old sighted male who developed a disordered day–night rhythm and was diagnosed with Hodgkin’s lymphoma. Laboratory examination revealed that the circadian rhythm of melatonin was disrupted in this patient (Garbazza et al., 2016). Moreover, the circadian rhythm of melatonin was disordered in a lymphoma patient with the levels of melatonin being much lower than in healthy subjects. These findings, although they do not prove an association, are consistent with the notion that low melatonin levels may predispose to haematological malignancies.

Some retrospective clinical studies have reported a relationship of melatonin disruption with haematological neoplasms. In 37 chronic lymphocytic leukaemia (CLL) patients, serum melatonin levels were significantly lower than those in an equal number of age- and sex-matched healthy volunteers ($P < 0.05$). In this case, the assay used was the human melatonin ELISA. Melatonin levels of shift workers with CLL patients were significantly lower than those in non-shift workers with CLL ($P < 0.0001$). Rana et al. (2014b) also reported that serum melatonin levels were markedly lower in CLL subjects, compared with healthy controls ($P < 0.0001$) and levels were found even more depressed in shift workers as compared to non-shift workers in CLL group ($P < 0.01$). These findings are consistent with the possibility that shift work may relate to the aetiology of CLL by perturbing the circadian secretion of melatonin (Rana et al., 2014a). In Canada, Parent et al. (2012) performed a population-based case–control study that enrolled 3137 males with incident cancer and 512 healthy controls. Compared to the men who never worked at night, the adjusted odds ratio of non-Hodgkin’s lymphoma (NHL) among men who ever worked at night are 2.31, suggesting that disrupted melatonin secretion is a potent etiological factor for haematological neoplasms (Table 1).

### Function of melatonin in haematological neoplasms

#### Apoptosis

Apoptosis is a pathophysiological process of programmed cell death in multicellular organisms (Jiang et al., 2016; Jiang et al., 2017; Li et al., 2017). Resistance to cell death is one of the most important characteristics of a tumour. Therefore, apoptosis is a pivotal mechanism for restraining tumour progression and several studies have demonstrated that melatonin promotes apoptosis of myeloid leukaemia cells. Rubio et al. (2007) reported that melatonin enhances cytochrome c release from mitochondria, augments activity of caspase-3, caspase-9, and down-regulates Bcl-2 in cancer cells. They also tested whether the apoptotic actions of melatonin in HL-60 cells are mediated by the classic membrane MT receptors and discovered that a non-specific MT receptor antagonist did not reverse the effects mentioned above, suggesting that the apoptotic response of myeloid leukaemia cells to melatonin is independent of these receptors. The combination of melatonin and puromycin represses the expression of anti-apoptotic proteins (Bcl-2 and Bcl-xL) and enhances activity of caspase-3 and cleavage of PARP compared to puromycin alone in human leukaemia HL-60 cells. This suggests that melatonin may be effectively used in leukaemia patients as a potential chemotherapeutic agent (Koh et al., 2011). Melatonin induces a significant increase in caspase-3 and -9 activities and evokes depolarization of the mitochondrial membrane and activation of permeability transition pore, thereby leading to elevated apoptosis of HL-60 cells as determined by propidium iodide positive-staining. These workers also discovered that melatonin-induced apoptosis is time-dependent and reaches to a maximum at 12 h and a minimum at 72 h (Bejarano et al., 2009). Jang et al. (2009) used

<table>
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<tr>
<th>Patients</th>
<th>Managements/phenomenal description</th>
<th>Effects/discovery</th>
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<tbody>
<tr>
<td>Thirty-seven CLL patients (Rana et al., 2014b)</td>
<td>Serum melatonin concentrations were determined by ELISA.</td>
<td>Significantly lower serum melatonin levels were observed in CLL patients compared to healthy subjects.</td>
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<td>A 40-year-old sighted male with Hodgkin’s lymphoma (Garbazza et al., 2016)</td>
<td>Patient had misalignment of the internal clock with the external light–dark cycle.</td>
<td>The circadian rhythm of melatonin was disrupted, and the levels of melatonin were low compared to healthy subjects.</td>
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<tr>
<td>Thirty-seven CLL patients (Rana et al., 2014a)</td>
<td>Aberrant expression of circadian clock and cell cycle genes (melatonin) were detected by ELISA.</td>
<td>Serum melatonin levels were remarkably low in CLL subjects compared to healthy controls, and levels were still lower in shift-workers compared to non-shift-workers in CLL group.</td>
</tr>
<tr>
<td>A total of 3137 males with incident cancer and 512 healthy controls (Parent et al., 2012)</td>
<td>Population-based case–control study.</td>
<td>Adjusted odds ratio of low-grade NHL among men with night work was 2.31 similar to controls.</td>
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both normal mice splenocytes and Jurkat T-leukaemia cells subjected to 2 Gy X-ray radiation. Pretreatment with 250 mg·kg⁻¹ melatonin enhanced the radiation-induced apoptosis of leukaemia cells while inhibiting radiation-induced apoptosis in normal mouse splenocytes, as shown by the reduced Bax/Bcl-2 ratio and p53 RNA in normal splenocytes. This suggests that melatonin may promote radiation-induced apoptosis via p53 expression. The apparent differential action of melatonin on radiation-induced apoptosis in normal and cancer cells provides an opportunity to increase the therapeutic ratio between tumour control and protection of normal cells in radiotherapy (Dong et al., 2016).

Melatonin also promotes apoptosis of acute lymphocytic leukaemia (ALL). Melatonin (10⁻³ M concentration) may induce the apoptosis of MOLT-4 cells by promoting the production of ROS, concomitant with reduced levels of GSH and GSH disulfide. Notably, they discovered that 10⁻⁵ M melatonin fails to induce the apoptosis of MOLT-4 cells (Buyukavci et al., 2006). Melatonin promoted apoptosis of leukaemia Molt-3 cells by increasing the activities of caspase-3, 6, 7 and 9, which are associated with an elevation of Bax and the release of cytochrome c from mitochondria; this documents that melatonin induces apoptosis of ALL cells through a caspase-dependent pathway (Perdomo et al., 2013). An above-normal level of apoptosis is also observed in human leukaemia REH cells after pretreatment with melatonin and this rise correlates with increased expression of Fas, death receptor (DR) 4, DR5 and their ligands. Thus, melatonin may find utility as a potential anti-ALL agent (Casado-Zapico et al., 2011).

Apart from leukaemia, melatonin also induces apoptosis of lymphoma cells. Sanchez-Hidalgo et al. (2012) reported that apoptosis appears, with an increased caspase-3 and PARP cleavage, within 0.5–1 h after melatonin treatment in three types of malignant Burkitt’s lymphoma cells (Ramos and DoHH2 cells); this response correlated with a breakdown of the inner mitochondrial transmembrane potential. They also discovered that Ramos cells are the most sensitive to melatonin, but an explanation for this differential response was not uncovered (Sanchez-Hidalgo et al., 2012). Paternoster et al. (2009) compared normal lymphocytes with lymphoma cells and discovered that melatonin is likely to induce apoptosis of lymphoma cells via ROS production. Moreover, melatonin causes apoptosis of RAMOS-1 lymphoblastoid cells, a response that was associated with down-regulation of Bcl-2, mitochondrial membrane depolarization, cytochrome c release and activation of caspase-3 (Trubiani et al., 2005). Collectively, the data summarized here demonstrate that melatonin should be considered a drug candidate for haematological neoplasms.

**Anti-proliferation**

Proliferation is a physiological process characterized with increased cell division and cell numbers. Unlimited proliferation is a unique feature of tumours and often causes immense damage to normal growth of the surrounding cells. Previous evidence has suggested that melatonin inhibits the proliferation of different tumours including lymphocytic leukaemia. Melatonin displays anti-proliferative properties in human Molt-3 leukaemia cells arresting the cell cycle. The reported findings document a significant arrest at G1 phase at 12 h after treatment, followed by rise in the number of hypodiploid cells at 24 h (Perdomo et al., 2013). Melatonin also causes the arrest at G1 phase of the cell cycle in Ramos, DoHH2 and SU-DHL-4 cells, associated with a reduction in the proportion of cells in the S and G2/M phases (Reiter et al., 2014b). The anti-proliferative effects of melatonin (at 10⁻³ M concentration) were readily apparent in CMK, Jurkat and MOLT-4 cells. Melatonin also restrains proliferation of tumour cells by inducing the production of ROS, which are cytotoxic to leukaemia cells (Buyukavci et al., 2006).

Melatonin also exerts anti-proliferative actions on myeloid leukaemia. Rubio et al. (2007) reported that melatonin suppressed the growth of the human myeloid leukaemia HL-60 cells by blocking the progression from G1 to S phase, which was accompanied by a significant inhibition of cell growth and reduced cell number. Melatonin induces the phosphorylation of p53 at Ser15 and restrains cell proliferation in PML cells. The group also showed that melatonin-induced anti-proliferative actions are mediated by p38 MAPK signalling (Santoro et al., 2012). Clearly, melatonin is a powerful anti-proliferative agent for haematological neoplasms.

**Pro-oxidation**

Pro-oxidation is associated with elevated levels of oxidative stress. As discussed above, melatonin is a powerful antioxidant in otherwise normal cells, but it becomes pro-oxidant in tumour cells (Bizzarri et al., 2013; Zhang and Zhang, 2014). The experimental data confirm that the antineoplastic effects of melatonin are attributed to its ability to induce free radical generation and oxidative stress (Ghibelli et al., 1998; Bizzarri et al., 2013). Melatonin stimulates the production of ROS and elevates the oxidizing environment in human myeloid HL-60 cells, with cytotoxic effects (Bejarano et al., 2011). For example, melatonin increases the activity of enzymes (lipoxygenase or cyclooxygenase) and promotes the production of ROS in Burkitt lymphoma BL41 cells (Paternoster et al., 2009). Similarly, the indole combined with 4 Gy X-ray irradiation causes a significant rise in ROS in Jurkat cells and enhances radiation-induced cell death via a pro-oxidant pathway (Jang et al., 2009). Thus, melatonin is a documented pro-oxidant molecule in haematological neoplasms.

**Immunomodulation**

The attack on tumour cells by the immune system is a dynamic and constant process throughout tumour growth including progression and metastasis (Diken et al., 2017; Porter and Raviprakash, 2017). Melatonin is also a modulator of immune cell function and haematopoiesis (Miller et al., 2006; Carrillo-Vico et al., 2013). Physiologically, melatonin is associated with T-helper 1 (Th1) cytokines and induces activation of Th1. In both normal mice and those with acute mid-stage erythroleukaemia, melatonin administration results in a quantitative and functional enhancement of natural killer (NK) cells, which mediate endogenous defences against cancer cells. Melatonin regulates cell dynamics of host defence, including the proliferative and maturational stages of haematopoietic and immune cells (NK cells, T and B lymphocytes, granulocytes and monocytes), thereby improving their normal physiological function. Notably, in mice bearing mid-stage leukaemia, daily administration of melatonin results in a survival index of 30–40% (more than 3 months) compared with 0% in untreated mice (Miller et al., 2006).
Melatonin ameliorates toxicity of anti-haematological malignancy drugs

Myelotoxicity, also known as myelosuppression, is the decrease of haematopoietic cells and haemocytes, which results from chemotherapy (e.g. imatinib) during the treatment of these neoplasms and other drugs that restrain the immune system (e.g. azathioprine) (Kantarjian et al., 2006; Hirbe et al., 2007; Von Hoff et al., 2013). Doxorubicin and cytarabine are two classical drugs used to treat haematological malignancy but they cause considerable haemotoxicity. Melatonin attenuates the reduction of marrow granulocyte macrophage-colony forming unit, CD3+, CD4+ and CDS+ splenic T-lymphocytes after doxorubicin treatment, concomitant with increased total GSH and reduced lipid peroxidation (Rapozzi et al., 1998). Melatonin reverses the fall in red blood cells, total leucocytes and platelets after cytarabine treatment. Additionally, melatonin significantly increases the amount of total protein, globulin and reduces the albumin/globulin ratio. These findings indicate that melatonin protects marrow and lymphoid tissue from injury by cytotoxic drugs as well as stimulating marrow regeneration (Nakayashiki et al., 2001). Moreover, melatonin protects the myeloid and erythroid series against intercellular oxidative stress induced by H2O2 during or 1 h after doxorubicin treatment (Greish et al., 2005).

Melatonin also ameliorates extra-haematotoxicity of anti-haematological malignancy drugs. Procarbazine is an effective chemotherapeutic drug especially in lymphoma whereas the testicular toxicity that induces sterility is a limiting factor. Melatonin in combination with this drug significantly lowers the levels of malondialdehyde and increases the levels of antioxidant enzymes, including GSH peroxidise, and nitrite values while exhibiting no side effects. These effects correlated with increased testicle size as indicated by their length, weight and sperm count (Alp et al., 2014). Methotrexate is widely used as a chemotherapeutic agent for leukaemia. The efficacy of this drug is often limited by intestinal mucositis in children and adults. Pretreatment with melatonin significantly attenuates methotrexate-induced oxidative stress and restores the activities of the antioxidant enzymes (GSH reductase and superoxide dismutase), thereby ameliorating methotrexate-induced small intestinal mucositis. This shows that melatonin protects against methotrexate-induced mucositis in humans with leukaemia (Kolli et al., 2013). Together, melatonin not only acts as an antineoplastic drug but also a protector against the toxicity of anti-haematological malignancy drugs. These results are consistent with other publications, which show that melatonin is an effective countermeasure to the molecular damage that is a consequence of many chemotherapies (Reiter et al., 2002).

Further perspectives

Drug synergy of melatonin

Melatonin is an endogenous molecule with low toxicity and favourable compatibility. When given in combination with other drugs, melatonin may improve their beneficial effects...
on haematological neoplasms (Oka et al., 1997; Orendas et al., 2014). Most of the published cases of combined therapy are focused on NHL. Patients with high-grade NHL that receive autologous stem cell transplantation (auto-SCT) usually relapse and have a poor prognosis. However, the combination of melatonin with cyclophosphamide, somatostatin, bromocriptine, retinoids or adrenocorticotropic hormone in patients with high-grade relapsing NHL after auto-SCT, allowed them to recover completely and to function normally at home (Todisco et al., 2001; Todisco, 2006; Todisco, 2009). The beneficial effects were also confirmed by Todisco’s group, who reported that a patient with advanced low-grade NHL recovered after a similar combination of drugs (Todisco, 2007). The Di Bella Method (melatonin, retinoids, vitamins C, D₃ and E, somatostatin and prolactin inhibitors) prolonged the 1, 3 and 5 year survival rates and improved the quality of life in 55 subjects with lymphoma, concomitant with low toxicity during the therapeutic process (Di Bella et al., 2012).

**In vitro**, incubation with 200–1000 pg·mL⁻¹ melatonin caused a significant and dose-dependent partial sensitization in doxorubicin-resistant P388 mouse leukaemia cells as shown by increased survival times of these cells. Interestingly, melatonin affects membrane P-glycoprotein and elevates intracellular concentrations of doxorubicin in leukaemia cells (Granzotto et al., 2001) (Table 2).

Radiotherapy is a particular therapeutic method for haematological neoplasms (Johansen et al., 2017). A combination of melatonin with 4 Gy irradiation induced apoptosis of Jurkat leukaemia cells in C57BL/6 mice, concomitant with prolonged lifetime of the leukaemic animals. Thus, melatonin enhances radiation-induced apoptosis and promotes survival of Jurkat leukaemia cells (Jang et al., 2009). It seems clear that the combination of melatonin with other oncostatic agents or radiation may be a promising method for improving the therapeutic efficacy and prolonging the lifespan of patients with haematological neoplasms (Figure 2).

**Other beneficial actions**

Although the study outcomes have been justifiably questioned, epidemiological studies have claimed an association between exposure to extremely low frequency electromagnetic fields and an increased risk of haematological neoplasms (Yellon, 1994). One proposed mechanism is that the power frequency fields may suppress the nocturnal production of melatonin, thereby contributing to a disturbed in-

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**Table 2**

Drug synergy of melatonin

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<tr>
<th>Patients/cells</th>
<th>Drug synergy</th>
<th>Results</th>
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<tbody>
<tr>
<td>Eight patients with relapsed low-grade NHL (Todisco, 2006)</td>
<td>Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH</td>
<td>Patients recovered completely and did normal activities at home.</td>
</tr>
<tr>
<td>Twenty patients with relapsed low-grade NHL (Todisco et al., 2001)</td>
<td>Melatonin, somatostatin, prolactin, retinoids and ACTH</td>
<td>Therapy was well tolerated and effective in 70% of these patients, concomitant with a mild toxicity.</td>
</tr>
<tr>
<td>Four patients with untreated progressive stage I CCL (Todisco, 2009)</td>
<td>Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH</td>
<td>No patients had recurrence and all did normal activities at home.</td>
</tr>
<tr>
<td>Twelve patients with low-grade stage IV NHL (Todisco, 2007)</td>
<td>Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH</td>
<td>All patients had complete remission and did normal activities.</td>
</tr>
<tr>
<td>Resistant P388 mice leukaemia cells (Granzotto et al., 2001)</td>
<td>Melatonin and doxorubicin</td>
<td>Melatonin mediated membrane P-glycoprotein and elevated intracellular concentrations of doxorubicin in leukaemia cells.</td>
</tr>
</tbody>
</table>
ternal environment and increasing risk of haematological malignancy (Henshaw and Reiter, 2005; Henshaw et al., 2008). Flight personnel are often exposed to the non-visible, low-frequency electromagnetic fields and often have disrupted sleep patterns, which depend on normal melatonin rhythm. Buja et al. (2005) searched the online databases of male flight attendants and discovered that meta-standardized incidence ratio of NHL was 2.49 (1.03–6.03) in these individuals and claimed that this was associated with low levels of circulating melatonin, suggesting that melatonin disruption is closely related to haematological malignancy. Nevertheless, the decrease of melatonin induced by occupational or environmental exposure to electric field is considerable (Kheifets et al., 1997; Ahlbom et al., 2001; Kheifets et al., 2009). Thus, maintenance of melatonin at normal levels might prevent haematological carcinogenesis.

Drug resistance remains a serious clinical problem in leukaemia therapy. Yamanishi et al. (2015) established two clofarabine-resistant lymphoblastic leukaemia cell lines and discovered that clofarabine-resistant cells exhibit a markedly reduced expression of mRNA for 2-deoxycytidine kinase after melatonin treatment. Meanwhile, histone acetylation of H3 and H4 was significantly lowered in resistant cells, as shown by the chromatin immunoprecipitation assay. Overall, melatonin treatment leads to significantly increased cytotoxicity with clofarabine in resistant cells via elevated acetylation, indicating that melatonin may be a useful candidate for overcoming resistance to drugs with anti-haematological neoplasm actions (Yamanishi et al., 2015) as has been shown for other drug-resistant tumours (Martin et al., 2010; Alonso-Gonzalez et al., 2015). During the therapy of promyelocytic leukaemia, melatonin also triggers the over-phosphorylation of p53 and prevents accumulation of damaged DNA in normal cells, thereby ameliorating the carcinogenic potential of normal cells (Santoro et al., 2012). Additionally, melatonin prevents the fall in bone marrow polychromatic erythroid, lymphocytes and neutrophils in lead-treated rats. Notably, it also attenuates the dyserythropoiesis and megaloblastic lesion in the marrow, indicating that melatonin has the ability to protect haematopoietic cells from lead-related toxicity (Othman et al., 2004). Again, these findings are consistent with the ability of melatonin to reduce lead-mediated toxicity in other organs. Collectively, melatonin may well be a general protective molecule in the haematological system.

Contrary data regarding the efficacy of melatonin as an inhibitor of haematopoietic cancer

Throughout this report, we have summarized studies showing that melatonin reduces the growth of haematological neoplasms. Some publications, however, question the beneficial role of melatonin in haematological neoplasms and suggest otherwise. Several studies have reported increasing melatonin serum levels in patients with cancers of haematological origin. Plasma melatonin concentrations were determined in 46 patients with multiple myeloma and 31 age-matched healthy subjects. The patients with multiple myeloma had significantly higher mean serum levels of melatonin than those in healthy subjects (22 ± 13.5 vs. 12 ± 4.8 pg·mL⁻¹; P < 0.001) (Tarquini et al., 1995). Lissoni et al. (1987) enrolled 42 patients with solid tumours and 21 patients with lymphoma or leukaemia. They also noted that all patients had significantly higher serum levels of melatonin than those in control subjects. Additionally, there are reports claiming that melatonin accelerated the proliferation of lymphoma (Conti et al., 1992) and leukaemia (Sakano et al., 2004) and restrained apoptosis of lymphoma cells (Tanyi, 2006). One report argued that melatonin per se has no relationship with haematological neoplasms (Touitou and Selmaoui, 2012), and the review of the literature suggested that any relationship between magnetic field exposure and melatonin suppression was questionable (Touitou and Selmaoui, 2012). These contradictory findings are not easily reconciled. Tarquini et al. (1995) predicted that the elevated levels of melatonin in patients with haematological neoplasms are a consequence of compensatory rise of melatonin in an attempt to inhibit tumour growth. While the majority of findings confirm a suppressive effect of melatonin on cancers of haematopoietic origin, there are clearly some that do not support that conclusion.

Perspectives

Haematological neoplasms are still a major problem that concerns many medical professionals. So far, there is little evidence for a role of the MT receptors in haematological neoplasms. Sanchez and Rubio found that the effects of melatonin against haematological neoplasms were independent of MT₁ and MT₂ receptors, although they did not give a clear alternative explanation (Rubio et al., 2007; Sanchez-Hidalgo et al., 2012). However, melatonin may increase the expression of the death receptors Fas, DR4 and DR5, thereby promoting the apoptosis of tumour cells (Rubio et al., 2007; Casado-Zapico et al., 2011; Zheng et al., 2013). Based on the reports summarized here, we feel that melatonin is a potentially important agent for the treatment of these tumours. Chemotherapy is currently the main treatment for haematological neoplasms, but such compounds have marked side effects and so melatonin may be more effective as a treatment and, when combined with conventional chemotherapies, may significantly reduce their side effects (Reiter et al., 2002; Buyukavci et al., 2011). Melatonin receptor agonists have been developed and include ramelteon (Pandi-Perumal et al., 2009) and agomelatine (Millan et al., 2003), but their indications are for sleep disorders only and whether they have any anti-cancer actions has not been tested. Clinical trials using melatonin to treat haematological neoplasms have not been carried out and the evidence from animal experiments remains sketchy. New directions of melatonin research should involve the following: (i) evaluating the actions of melatonin alone on haematological neoplasms including defining melatonin’s molecular effects on these cancers for providing a better treatment strategy; and (ii) using a combination of melatonin with chemotherapies to possibly increase their efficacy. Moreover, possibly of even greater importance would be the use of melatonin to reduce the toxicity of commonly used drugs to treat haematological cancers.
Concluding remarks

As summarized in this review, melatonin appears to have beneficial actions against haematological neoplasms, overall. The normal circadian pattern of secretion of melatonin from the pineal gland may determine its protective actions against haematological cancers. The positive effects of melatonin are pro-apoptotic, pro-oxidative, anti-proliferative and immunomodulatory. Thus, the timing of exogenous melatonin administration may be critical in determining its efficacy as an oncostatic agent. Importantly, melatonin also ameliorates the toxicity of many drugs used to treat haematological malig-nancies, including myelotoxicity and toxicity on non-haematological tissues. Finally, clarification of the intracellular signalling network of melatonin’s anti-neoplastic actions will help to facilitate further basic research and clinical application of melatonin in the treatment of haematological neoplasms.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander et al., 2015a,b,c,d,e).

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Conflict of interest

The authors declare no conflicts of interest.

References


Lissoni P, Bolis S, Brivio F, Fumagalli L (2000). A phase II study of neuroimmunotherapy with subcutaneous low-dose IL-2 plus the...
pinea...n oncogene for non-small-cell lung cancer. Oncotarget 7: 46768–46784.


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targeted epidermal growth factor receptor mutation to the tyrosine kinase inhibitor gefitinib. Cell Physiol Biochem 34: 865–872.

