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Themed Section: Recent Developments in Research of Melatonin and its Potential Therapeutic Applications

REVIEW ARTICLE

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.

LINKED ARTICLES

This article is part of a themed section on Recent Developments in Research of Melatonin and its Potential Therapeutic Applications. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v175.16/issuetoc

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

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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 haematonosis but such chemotherapy agents may also have serious adverse effects such as respiratory distress, pulmonary infiltrates, renal and cardiac failure (Frankel *et al.,* 1992). Although 90% of patients with acute promyelocytic leukaemia (APL) may improve after treatment with **all-trans retinoic acid** (tretinoin), this compound is used only for APL (Mantha *et al.,* 2017). Additionally, haematopoietic stem cell transplantation is an effective method for haematological neoplasms, especially leukaemia. However, the medical cost is high and immunological rejection is sometimes intense (Iwamoto *et al.,* 2014). Therefore, much effort has been devoted to searching for a novel drug (s) in order to overcome the deficiencies of these strategies.

Melatonin is an indoleamine derived from the pineal gland, which modulates circadian rhythms and participates in a wide range of physiological processes (Cagnacci, 1996; Carrillo-Vico *et al.,* 2013; Silvestri and Rossi, 2013; Cipolla-Neto *et al.,* 2014; Iwamoto *et al.,* 2014; Reiter *et al.,* 2014a; Manchester *et al.,* 2015; Reiter *et al.,* 2016). Notably, it has low toxicity in humans and other animals. In mammals, melatonin is produced by the pineal gland in the vertebrate brain and in numerous other organs (Sugden *et al.,* 2004; Reiter *et al.,* 2013; Acuna-Castroviejo *et al.,* 2014). The activation of two well-characterized G-protein-coupled seven-transmembrane-domain receptors, **MT1** and **MT_2**, inhibits cAMP formation through *Pertussis* toxin-sensitive inhibitory G proteins Moreover, activation of melatonin receptors might also promote the apoptosis of cancer cells and inhibit cancer development (Sanchez-Hidalgo *et al.,* 2012).

In 1917, McCord and Allen reported that feeding tadpoles macerated bovine pineal tissue lightened their skin by causing the accumulation of melatonin in epidermal melanophores. The pineal factor that causes the change in amphibian skin pigmentation was isolated from the bovine pineal gland in 1958 and identified as N-acetyl-5-methoxytryptamine (Lerner *et al.,* 1960). This compound was subsequently called melatonin and was found in all animals, plants, bacteria and fungi (Tan *et al.,* 2010, 2014; Acuna-Castroviejo *et al.,* 2014; Arnao and Hernandez-Ruiz, 2015; Erland *et al.,* 2015; Yu *et al.,* 2016). In mammalian pineal glands, melatonin synthesis is activated by daily onset of darkness, and, after its secretion, it affects sleep, mood and circadian rhythms (Santoro *et al.,* 2012; Yun *et al.,* 2014; Hill *et al.,* 2015; Xiang *et al.,* 2015; Borin *et al.,* 2016).

Earlier research documented that melatonin is a pivotal oncostatic agent in various tumours including haematological neoplasms (Santoro *et al.,* 2012), breast cancer (Hill *et al.,* 2015; Xiang *et al.,* 2015; Borin *et al.,* 2016), lung cancer (Yun *et al.,* 2014; Fan *et al.,* 2015), hepatocellular carcinoma (Ordonez *et al.,* 2015), gastrointestinal cancer (Wei *et al.,* 2015), renal cancer (Park *et al.,* 2014), pancreatic cancer (Ruiz-Rabelo *et al.,* 2011), uterine (Mao *et al.,* 2016), cervical cancer (Pariente *et al.,* 2016), neural cancer (Chen *et al.,* 2016) and melanoma (Cabrera *et al.,* 2010). Antineoplastic mechanisms of melatonin include proapoptotic, pro-oxidative, anti-proliferative and immunomodulatory actions. Also, *via* its actions as a potent antioxidant, melatonin has protective actions against myocardial ischaemia (Yang *et al.,* 2013; Yu *et al.,* 2014, 2015a, b, 2016), ischaemic stroke (Yang *et al.,* 2015), septic encephalopathy (Zhao *et al.,* 2015), subarachnoid haemorrhage (Dong *et al.,* 2016) and flow shear stress (Yang *et al.,* 2016). The melatonin-mediated anti-tumour effects have been reviewed for lung cancers (Ma *et al.,* 2016) and gastrointestinal cancers (Xin *et al.,* 2015), but information on its relationship to haematological neoplasms remains unsummarized.

Here, we have reviewed the publications related to the role of melatonin in haematological neoplasms, focusing on the therapeutic actions of melatonin against haematological cancers. 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 future 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 (Rana *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 restrains 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 1

Studies suggest a relationship of melatonin and haematological carcinogenesis

Patients	Managements/phenomenal description	Effects/discovery
Thirty-seven CLL patients (Rana *et al.,* 2014b)	Serum melatonin concentrations were determined by ELISA.	Significantly lower serum melatonin levels were observed in CLL patients compared to healthy subjects.
A 40-year-old sighted male with Hodgkin's lymphoma (Garbazza *et al.,* 2016)	Patient had misalignment of the internal clock with the external light–dark cycle.	The circadian rhythm of melatonin was disrupted, and the levels of melatonin were low compared to healthy subjects.
Thirty-seven CLL patients (Rana *et al.,* 2014a)	Aberrant expression of circadian clock and cell cycle genes (melatonin) were detected by ELISA.	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.
A total of 3137 males with incident cancer and 512 healthy controls (Parent *et al.,* 2012)	Population-based case–control study.	Adjusted odds ratio of low-grade NHL among men with night work was 2.31 similar to controls.

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 Ser^{15} 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 erythroleukemia, 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).

A high-dose cytotoxic chemotherapy is a commonly used treatment for patients with ALL and is partly effective (Lissoni *et al.,* 2000; Raj *et al.,* 2013). However, this therapy usually contributes to considerable side effects such as myelosuppression, which leads to a weakened immune system that is difficult to correct later. Relative to this serious problem, Lissoni *et al*. (2000) carried out a phase II study of low-dose **IL-2** plus melatonin in 12 patients with an untreatable advanced haematological malignancy, including NHL (six cases), Hodgkin's disease (two cases), multiple myeloma (two cases), acute myeloid leukaemia (AML; one case) and chronic myelomonocytic leukaemia (one case). IL-2 was injected subcutaneously at a dose of 3 million IU·day^{-1}, and melatonin was given orally at 20 mg·day^{-1} in the evening for 4 weeks. The results showed that tumour progression was markedly suppressed in eight patients and a median duration of survival was extended by 21 months (14–30 months) for these patients. This suggests that the combination of low-dose IL-2 plus melatonin may prolong the survival time in untreatable advanced haematological malignancy, compared to high-dose IL-2 toxic immunotherapy alone (Lissoni *et al.,* 2000). Extracts of *Echinacea purpurea* and melatonin elevated the number and activity of NK cells and enhanced the killing competence to tumour cells in leukaemia mice. Notably, the combination prolongs the lifespan of leukemic mice compared to melatonin alone (Currier and Miller, 2001). Taken together, the observations suggest melatonin-induced immunomodulation may be useful as an effective management for haematological neoplasms (Figure 1).

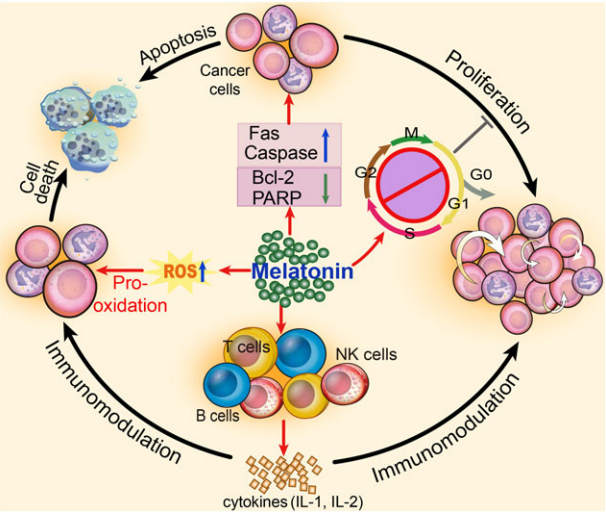

Figure 1

Roles of melatonin in haematological neoplasms. Melatonin is a pivotal endocrine compound, with actions against haematological carcinogenesis. Melatonin up-regulates the levels of Fas and caspase family and down-regulates the levels of PARP and Bcl-2, as well as enhancing the production of ROS for promoting the apoptosis of haematological cancer cells. Melatonin also blocks the cell cycle of cancer cells to inhibit their proliferation. Additionally, activity of immunocytes and secretion of cytokines can be enhanced by melatonin, thereby inducing immunomodulation against haematological neoplasms.

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 haematotoxicity. 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 H_2O_2 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, D_3 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).

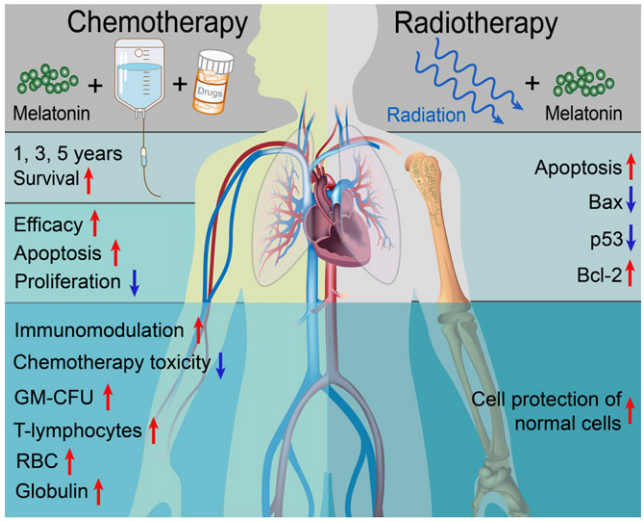

Figure 2

Actions of melatonin on chemo- and radiotherapy. Combination of melatonin with chemotherapeutic agents promotes survival, enhances the efficacy and immunomodulation and ameliorates toxicity due to chemotherapy, in patients with haematological neoplasms. Melatonin combined with radiotherapy promotes the apoptosis of haematological cancer cells while protecting the normal splenocytes, suggesting its selective cytotoxicity to haematological neoplasms.

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-

Table 2

Drug synergy of melatonin

Patients/cells	Drug synergy	Results
Eight patients with relapsed low-grade NHL (Todisco, 2006)	Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH	Patients recovered completely and did normal activities at home.
Twenty patients with relapsed low-grade NHL (Todisco *et al.,* 2001)	Melatonin, somatostatin, prolactin, retinoids and ACTH	Therapy was well tolerated and effective in 70% of these patients, concomitant with a mild toxicity.
Four patients with untreated progressive stage I CCL (Todisco, 2009)	Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH	No patients had recurrence and all did normal activities at home.
Twelve patients with low-grade stage IV NHL (Todisco, 2007)	Melatonin, cyclophosphamide, somatostatin, bromocriptine, retinoids and ACTH	All patients had complete remission and did normal activities.
Resistant P388 mice leukaemia cells (Granzotto *et al.,* 2001)	Melatonin and doxorubicin	Melatonin mediated membrane P-glycoprotein and elevated intracellular concentrations of doxorubicin in leukaemia cells.

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 MT_1 and MT_2 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 inthis 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 malignancies, 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.

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