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Review

Melatonin and Fertoprotective Adjuvants: Prevention against Premature Ovarian Failure during Chemotherapy

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Abstract: Premature ovarian failure is one of the side effects of chemotherapy in pre-menopausal cancer patients. Preservation of fertility has become increasingly important in improving the quality of life of completely recovered cancer patients. Among the possible strategies for preserving fertility such as ovarian tissue cryopreservation, co-treatment with a pharmacological adjuvant is highly effective and poses less of a burden on the human body. Melatonin is generally produced in various tissues and acts as a universally acting antioxidant in cells. Melatonin is now more widely used in various biological processes including treating insomnia and an adjuvant during chemotherapy. In this review, we summarize the information indicating that melatonin may be useful for reducing and preventing premature ovarian failure in chemotherapy-treated female patients. We also mention that many adjuvants other than melatonin are developed and used to inhibit chemotherapy-induced infertility. This information will give us novel insights on the clinical use of melatonin and other agents as fertoprotective adjuvants for female cancer patients.

Keywords: melatonin; chemotherapy; fertoprotective adjuvant; premature ovarian failure

1. Introduction

The most significant and common side effects of chemotherapy include infertility and premature ovarian failure (POF) [1]. Therefore, prevention of POF and protection of the ovarian follicle pool have gained increasing attention to improve the quality of life of female cancer patients receiving chemotherapy. Major international guidelines recommend that physicians should discuss with their female cancer patients at risk of chemotherapy-induced POF and ovarian dysfunction, and help with the decision of fertility preservation as early as possible [2–4]. Among the strategies for preservation of fertility, cryopreservation of a piece of ovarian tissue or premature oocyte is commonly considered. However, these methods are limited because of several factors such as time, cost, and gonadotoxic potential attributable to storage procedures [2,4]. Protective adjuvants that can protect the dormant follicle pool and prevent follicle loss during chemotherapy would provide considerable advantages over current fertility preservation strategies, in that they would be appropriate for young patients.

Until recently, because of the lack of understanding of the mechanism underlying the side effects of an anticancer drug, there had been limited improvement in the field of ovarian fertility preservation. However, many patients experience chemotherapy-induced side effects, and the need to preserve fertility has been repeatedly highlighted by physicians. In this brief review, we summarize the

mechanisms and reports demonstrating the role of melatonin as a fertoprotective adjuvant that suppresses chemotherapy-induced dormant follicle activation and preserves the follicle reserve. The data suggest that melatonin could be a potential agent in the field of fertility preservation for chemotherapy-treated female cancer patients.

2. Chemotherapy-Induced Ovarian Disorder

Chemotherapy remains the standard of care for cancer, and could damage various organs depending on the age and sex of patients and dose of agents [5–7]. Chemotherapeutic agents inhibit vital processes of cells, thereby arresting cell proliferation, and inducing abnormal activation of the dormant follicles in the ovary. Previous studies have reported that anticancer drug treatment induces varying levels of ovarian damages, resulting in repression of fertility [8,9], and presented solutions to ameliorate ovarian atrophy and prevent the loss of follicle reserve and infertility [1,10,11]. Although older women have a lower follicle pool and are more susceptible to POF than young women [6] due to chemotherapy-induced apoptosis of somatic cells in growing follicle and fibrosis of stromal blood vessel in the ovary [9,11], burn-out of dormant follicle pool is still significant [12,13].

2.1. Chemotherapeutic Drugs

Several groups of anti-cancer drugs classified based on their type and action are listed below. First, alkylating molecules, such as cyclophosphamide, have significant damaging effects on ovarian tissue [14–16], and are responsible for the highest rates of age-related ovarian failure [12]. Second, platinum-based molecules, such as cisplatin, cause amenorrhea [17,18], and induce DNA damage in the ovary through c-Abl tyrosine kinase inhibition and p63 activation [19,20]. Cisplatin also induces aneuploidy in oocytes and early embryonic death [21]. Third, anthracycline compounds such as doxorubicin induce oxidative stress in mature/premature oocytes and trigger dominant lethal mutations and aneuploidy [22]. Clinical data indicate that doxorubicin has an intermediate or a lower risk than that of other chemotherapeutic agents [12,23]. However, Hortobagyi et al. reported that the frequency of amenorrhea was much higher in women older than 30 years who received doxorubicin treatment (33% in women aged 30–39-years, and 96% in women older than 40 years) than in those younger than 30 years [24]. Fourth, vinca alkaloids such as vinblastine induce a high level of aneuploidy in an animal model [22], but a clinical study reported a reduced risk of ovarian failure [25,26]. Fifth, anti-metabolites such as methotrexate and 5-fluorouracil do not affect fertility; however, data regarding this are limited [27]. One of the anti-metabolites, methotrexate is generally used to treat ectopic pregnancy without any agent-related side effect [28,29]. Sixth, the effects of taxane family-related drugs such as paclitaxel on fertility are controversial. Several studies have suggested low or no risk of amenorrhea [30–34], whereas other studies reported gonadal toxicity as indicated by high follicle stimulating hormone (FSH) levels [9] and an increasing risk of amenorrhea [32,35]. Finally, biological targeted therapy is a novel form of chemotherapy and comprises drugs such as tamoxifen or herceptin that interfere with specific factors expressed by cancer cells. Because it has only recently been used to treat tumor cells and designed to target specific cancer cells, there are fewer data on its effects on the ovary. Therefore, these agents are mostly used as therapeutic adjuvants after initial chemotherapy due to their fewer side effects and low risk on the fertility [36]. However, additional clinical data and studies are necessary. Patients are often treated with the above-mentioned agents and their combinations, but it is difficult to predict ovarian damage due to inter-individual variations [12,37]. A combination of adriamycin, bleomycin, dacarbazine, and vincristine for lymphoma is reported to be less ovotoxic [38–40], whereas another major combination of cyclophosphamide, procarbazin, prednisone, and vincristine induces POF [41,42]. In order to understand the mechanism of POF induced by chemotherapy, it is necessary to accumulate clinical data continuously.

2.2. Mechanisms of Chemotherapy-Induced Ovarian Disorder

Anticancer drugs induce DNA damage or inhibit cell division, eventually leading to cell apoptosis. In the ovary, DNA damage, such as DNA double-strand breaks, induced by chemotherapy activates apoptosis of somatic granulosa cells and oocytes [43–45]. In addition, chemotherapy stimulates abnormal activation of dormant primordial follicles, leading to POF [1,27,46,47]. The response and reaction of chemotherapy agents depend on cells. Therefore, understanding the signal transduction and mechanisms of chemotherapy agents is important for preserving germ cells in the ovary.

The toxic effect of chemotherapy on dormant primordial follicles is not clearly studied, whereas it has been demonstrated that anticancer drugs induce apoptosis of oocytes and somatic cells such as granulosa and cumulous in large follicles [20,21,43,48]. Oktem and Oktay reported that cyclophosphamide rapidly decreases the number of primordial follicles and induces apoptosis in a human-mice ovarian xenograft model [49]. In vitro ovarian culture showed that spontaneous activation of primordial follicles is stimulated by chemotherapeutic agents in animals [50] and humans [51]. Recently, Xiang et al. reported that cyclophosphamide, an alkylating molecule, induces dormant follicle pool depletion by indiscriminately activating primordial follicles without inducing death, leading to the induction of POF [52]. Cisplatin, a platinum-based agent, also strongly triggers activation of primordial follicles without inducing follicle death [53,54].

Two main pathways explain how the primordial follicles in the ovary die or are activated. One is the tumor suppressor protein TP53 (known as p53)-dependent pathway. TP53 has been reported to be involved in apoptosis of ovarian granulosa cells in rats [55,56]. Conversely, Depalo et al. showed that TP53 protein is less expressed in human ovarian follicles [57]. An anticancer drug, doxorubicin did not stimulate apoptosis of mature oocytes in *TP53*-deficient mice [58]. These suggest that the mechanisms of TP53-mediated follicle apoptosis and chemical-induced DNA damage are independent of each other. Recently, several studies demonstrated that TAp63, a homolog of TP53, is present in the nucleus of oocytes [59] and is a master regulator of DNA damage or repairing system in the oocyte of primordial follicles [60,61]. When TAp63 is lacking, oocytes exhibit resistance to radiation-induced DNA damage [60]. Additionally, p53-upregulated modulator of apoptosis (PUMA) and Phorbol-12-Myristate-13-Acetate-Induced Protein 1 (NOXA) play an important role in regulating downstream factors in the TAp63 signaling pathway in DNA-damaged oocytes [62]. The regulator of TAp63 transcribes c-Abl tyrosine kinase, which maintains genomic integrity by regulating DNA status in cells [63]. c-Abl and TAp63 regulate apoptosis of cells exposed to chemotherapeutic agents such as cisplatin [20] and doxorubicin [64]. Kim et al. showed that cisplatin induces c-Abl and TAp73, another homolog of TP53, in ovaries [65]. In addition, Bolcun-Filas et al. reported that checkpoint kinase 2 (Chk2) is essential for surveilling and killing oocytes undergoing abnormal meiosis and harboring DNA double-strand breaks [66]. A further study is needed to determine whether checkpoint kinase 2 (CHK2) is regulated by anticancer drugs. However, the results of the existing studies suggest that CHK2 and TAp63 regulate crucial pathways via PUMA, NOXA, bcl2-associated X protein (BAX), TAp73, and c-Abl (Figure 1).

The other regulatory pathway is the PI3K-dependent signaling pathway. Various studies have shown that the activation of dormant follicles in the ovary is regulated by the PI3K/PTEN/AKT signal pathway in mice [67–70], and in a human in vitro model [71,72]. The balance of factors within the PI3K pathway is very important for determining the fates of dormant primordial follicles [73]. PTEN is a key negative regulator of the PI3K signaling pathway and plays critical roles in various tissues and cells [67,68,74–77]. AKT is activated by phosphorylation of the PI3K signaling pathway and phosphorylates downstream signal pathway proteins including forkhead box O3a (FOXO3a), glycogen synthase kinase (GSK), tuberous sclerosis 1/2 (TSC1/2), and bcl2 associated against of cell death (BAD) [53,70,73,78–80]. Anticancer drugs activate the PI3K/AKT signal pathway, which results in continuous activation of dormant primordial follicles causing POF during chemotherapy [81]. FOXO3a is an important transcriptional factor in the PI3K signaling pathway and regulates primordial follicle activation [82]. When a primordial follicle is activated, FOXO3a is phosphorylated and exported

from the nucleus to the cytoplasm [53]. In the nucleus, FOXO3a functions as a transcriptional activator to induce the expression of $p27^{Kip1}$, which encodes a cyclin dependent kinase (CDK) inhibitor protein for maintaining quiescence of primordial follicles [83,84]. In fact, the deficiency of $p27^{Kip1}$ results in excessive activation of primordial follicles leading to POF in mice [85]. The molecular pathway of PI3K signaling in the regulation of primordial follicle fate is summarized in Figure 2. Therefore, it is critical to understand the molecular mechanism of the PI3K pathway rather than that of the TP53 pathway and to find appropriate fertoprotective adjuvants to protect the activation of follicle reserve in the ovary during chemotherapy.

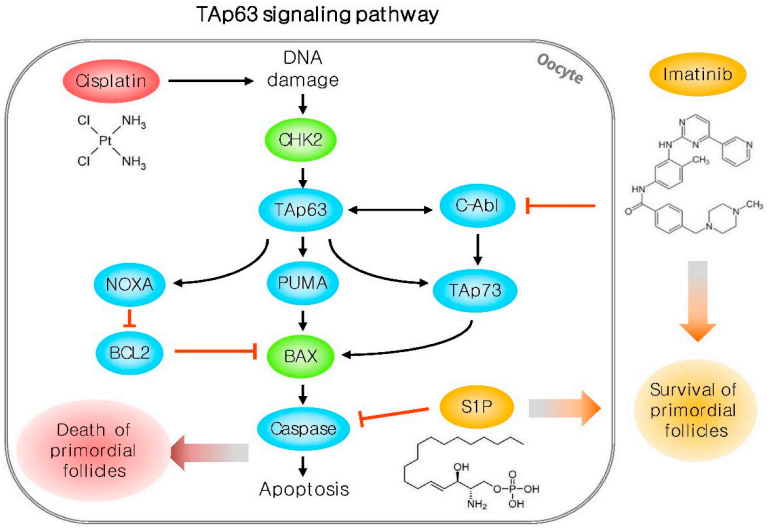

Figure 1. Schematic model for chemotherapy-induced oocyte death via the TAp63 signaling pathway. Cisplatin treatment causes DNA damage in oocytes and induces a surveillance factor, Chk2, followed by activation of NOXA, PUMA, and TAp73. Therefore, DNA-damaged oocytes undergo programmed cell death. However, imatinib and S1P rescue these DNA-damaged oocytes via inactivation of the TAp63 signaling pathway. Black arrow: activation; red T bar: suppression.

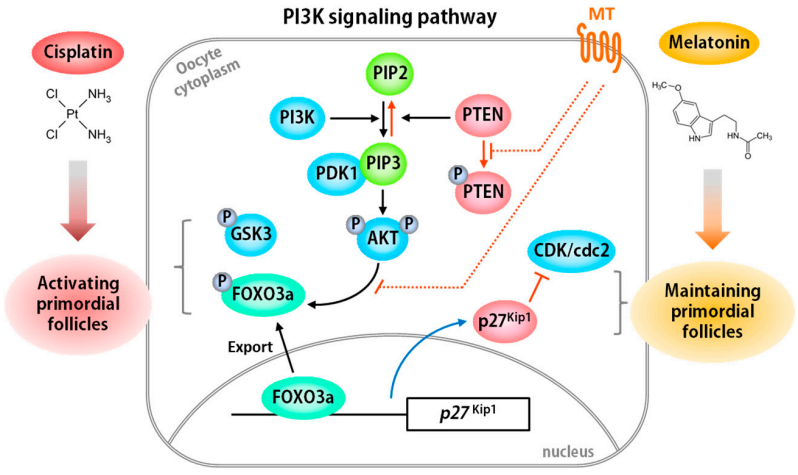

Figure 2. Schematic model for regulation of primordial follicle activation via the PI3K signaling pathway. Cisplatin induces activation of the PI3K/AKT/GSK/FOXO3a pathway via a phosphorylation cascade leading to activation of dormant primordial follicles. However, melatonin suppresses cisplatin-induced activation by inducing PTEN activity and inhibiting FOXO3a phosphorylation, thereby resulting in the expression of $p27^{Kip1}$, CDK inhibitor, during chemotherapy. Black arrow: activation; red T bar: suppression; dotted line T bar: possible inhibition; red arrow: inactivation; blue arrow: transcription.

3. Melatonin and Other Adjuvant Agents for Protection against Chemotherapy-Induced Follicle Depletion

3.1. Melatonin

3.1.1. Pleiotropic Effects of Melatonin on Cancer Prevention and Immune System

Melatonin (*N*-acetyl-5-methoxytryptamine) is primarily revealed as a secretory product of the pineal grand in vertebrates, and is a derivative of tryptophan [86]. Recently, it has been shown that melatonin is produced in various tissues including reproductive tissues such as ovary and placenta [87–91]. This molecule is lipophilic, and acts as an antioxidant and a free radical scavenger [92–97]; it is present in many biological fluids such as synovial fluid, amniotic fluid, cerebrospinal fluid, saliva, bile, and breast milk [98,99]. Several studies have reported that exogenous melatonin has protective effects in the kidneys [100,101], nerve system [96,102], lungs [103], ovaries [46], uterus [104,105], and testes [106], and against oxidative stress [107]. Melatonin level and production gradually decrease with age [108,109], and this status can be very important for the overall decrease in the quality of life of the elderly [110]. Other reports have shown that a decreasing level of melatonin is relevant to the development of various diseases [111,112], and that supplementation of melatonin improves the quality of life of the elderly and patients [113,114]. These imply that melatonin is a pleiotropic molecule modulating cellular response spatially and temporally.

Melatonin has been focused to be an anti-cancer agent as well as antioxidant via regulating various cellular mechanisms including cell proliferation and angiogenesis. First, melatonin can prevent cancer growth. In 2000, Mocková et al. reported an interesting paper that melatonin administration suppressed chemocarcinogen-induced mammary carcinogenesis [115]. Yousefi and colleagues reviewed recent studies about melatonin effect on the regulation of DNA damage response and repair [116]. In response to DNA damage response, a protein kinase, ataxia-telangiectasia mutated (ATM) activates DNA damage checkpoint resulting in apoptosis and senescence. Melatonin reduced radiation-induced DNA damage by suppressing ATM expression [117]. In addition, there are several key regulators such as p53 and p21 induced by DNA damage response which are involved in cell cycle arrest. Several studies showed that melatonin suppressed proliferation of cancer cells such as breast cancer cell line, MCF-7 (Michigan Cancer Foundation-7) and hepatocarcinoma cell line, HepG2 by activation of p53 and p21 pathway [118–121]. Phosphorylation of p53 at serine 15 residue (Ser-15) is important for the p53 activity against DNA damage. Santoro and colleagues demonstrated that melatonin induces p53 phosphorylation at Ser-15 residue and that melatonin preventing effect on DNA damage is mediated via melatonin receptor (MT) [122,123]. There are two types of melatonin receptor, MT1 and MT2 in mammals [124]. Melatonin receptors are G protein-coupled receptors, which play an important role in various cellular processes and drug responses [125]. Santoro et al. showed that melatonin activates p38 MAPK-dependent phosphorylation of p53 [122] and the signaling pathway is mediated by melatonin receptor [123]. Indeed, the phosphorylation of p53 is independent of ATM.

Secondly, melatonin is able to inhibit tumor growth by suppression of angiogenesis. Several reports demonstrated that the angiogenesis is prevented via decreasing the expression of endothelin converting enzyme-1 [126] and reducing the activation of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2) [127,128]. Recently, the anti-angiogenic effect of melatonin was proved in xenograft models of breast cancer [129]. They demonstrated that melatonin effectively reduced tumor growth and cell proliferation by the inhibition of angiogenesis. An interesting study recently reported that melatonin can seasonally control pituitary function by regulating the expression of VEGF and VEGFR2 in the pituitary. They showed that melatonin controls producing isoform type of VEGF and VEGFR2 resulting in angiogenesis modulation which is critical for hormone release of the pituitary depending on breeding season [130].

Thirdly, the immunomodulatory effect of melatonin in cancer was reviewed by Miller et al. in 2006 [131]. Melatonin can activate T-lymphocyte [132–134] macrophage [133], as well as cells of spleen [135], lymph node and bone marrow [136]. In addition, melatonin stimulates the production

of cytokines including interleukin (IL)-2, interferon (IFN)-γ and IL-6 [137,138]. Another effect of melatonin on immune system is to regulate tumor immunosurveillancers such as natural killer (NK) cells [139]. Melatonin treatment in leukemia model increased the number of NK-cells [140]. A recent report showed that melatonin can improve the activity of T-lymphocyte which was decreased in aged mice [141]. These imply that melatonin is able to enhance the immune system via production of cytokines leading to prevention of various cancers.

3.1.2. Melatonin as Antioxidant in Ovarian Follicles

Melatonin acts as a powerful antioxidant to prevent free radical damage by oxidative stress in the body. The oxidative stress causes various diseases including cancer, neurological disease, rheumatoid and reproduction [142–144]. The early ovarian follicle loss causes premature ovarian failure in premenopausal women. The primordial follicles during reproductive life have three fates: dormancy, activation, and atresia [145,146]. Most primordial follicles should be quiescent until activation for oocyte maturation. Once recruited and activated, the maturation of oocytes proceeds very rapidly. This dynamic process causes considerable oxidative stress. Tamura et al. reported that the oocyte quality was lowered by oxidative stress [147]. In fact, the follicular fluids contains significant amount of melatonin [148]. Several studies have reported that melatonin in ovarian fluid protects the oocytes and granulosa cells by ameliorating oxidative stress during ovulation which is critical for normal maturation [147–149]. In addition, the supplement of melatonin improves oocyte quality [147,150,151]. Interestingly, melatonin receptors (MT1 and MT2) are expressed in the ovary [152–154]. These suggested that melatonin acts as a scavenger via its receptor. Recent study demonstrated that melatonin treatment ameliorates premature ovarian failure by decreasing oxidative stress damage, which was mediated by SIRT1 signaling [151]. Of course, the effect of melatonin on the primordial follicles remains unclear. However, these imply that the ovarian melatonin might act regionally in the primordial follicles from dynamic oxidative stress during folliculogenesis.

3.1.3. New Application of Melatonin as a Fertoprotective Agent in Fertility Preservation

Many anti-cancer drugs including cyclophosphamide and cisplatin have been known to induce apoptosis of granulosa cells in the ovary and stimulate over-activation of dormant primordial follicles resulting in premature ovarian failure (POF) [1,27,43–47]. POF is one of the causes of female infertility. Fertility preservation of cancer female patients is very important for their life after cancer survival. Therefore, it has become important for finding a fertoprotective agent which protect germ cells and increase the efficacy of anti-cancer drug during chemotherapy. Interestingly, melatonin has various prospects as a potential therapeutic adjuvant during chemotherapy. The treatment of melatonin reduces the adverse effects of chemotherapy by removing superoxide anion, hydrogen peroxide, and peroxyl radical [155–159]. Several studies have demonstrated that melatonin treatment protects depletion of germ cells in the gonads during chemotherapy. In male reproductive organ, melatonin administration prevents cisplatin-induced testicular toxicity and reduces sperm motility [106]. Chang et al. showed that cisplatin induces the depletion of follicles via over-activating the dormant primordial follicles in the ovary [54]. They examined the protection effect of melatonin on cisplatin-treated ovaries. Combined treatment with melatonin and cisplatin significantly prevented primordial follicle loss in cisplatin-treated ovary. Recent reports give us a clue for the molecular mechanism of melatonin in the ovary. As mentioned above, melatonin signals through two types of melatonin receptors, MT1 and MT2 in mammals [124]. In fact, several studies supported that melatonin receptors are present in the oocytes and granulosa cells of various species ovary including human [154,160–163]. Melatonin receptors are G protein-coupled receptors, which play an important role in various cellular processes and drug responses [125]. Therefore, the protective effect of melatonin in follicles is thought to be achieved through the G protein-coupled receptor-dependent pathway (Figure 2). In 2016, Jang et al. demonstrated that the regulatory protection effect of melatonin is mediated by suppressing the activation of the PI3K/AKT/FOXO3a signaling pathway in cisplatin-treated ovary [53]. This suggests

that melatonin is directly involved in PI3K signaling via its receptor. The theory is supported by two reports. One is showing that melatonin induces AKT phosphorylation PI3K signaling pathway in astrocyte [164]. The other explained that melatonin mediates neuroprotective activity in ischemia via PI3K/PTEN/AKT signaling pathway [165]. In addition, the ovary can produce melatonin [148]. Follicular fluid in the growing follicles contains high level of melatonin [166,167]. The supplementation of melatonin for in vitro maturation of oocytes improves the oocyte quality [150,167]. These indicate that the endogenous melatonin is not enough for preventing chemo-induced primordial follicle loss in the ovary even though it is critical for oocyte development. The detail molecular mechanism of melatonin protective response against chemo-induced ovarian damage needs further studies.

3.2. Other Candidates as a Fertoprotective Agent

3.2.1. Sphingosin-1-phosphate

Sphingosin-1-phosphate (S1P) is derived from sphingolipids. Morita et al. firstly reported that S1P has a protective effect against oocyte apoptosis in radiation-induced ovary [168]. It is an anti-apoptotic agent that inhibits apoptosis through the sphingomyelin pathway, which was reported to be responsible for the death of ovarian follicles (Figure 1) [58,168]. However, the effect of S1P on the ovary is controversial. Treatment with S1P showed a protective effect against dacarbazin- [169], cyclophosphamide- and doxorubicin-treated ovarian follicles [170], but not against cyclophosphamide-treated ovary [171]. In addition, the administration of S1P during chemotherapy has some limitations. S1P treatment interferes with the clinical effects of anticancer drugs, and its anti-apoptotic effect may suppress the normal atresia of DNA-damaged oocytes during folliculogenesis. Recent studies reported that melatonin suppresses liver damage by rabbit hemorrhagic disease virus [172], and diethyinitrosamine-induced hepatic carcinoma in mice [173] by inhibiting sphingosine kinase/S1P signaling pathway. In addition, the suppressing effect of melatonin on chemical-induced S1P signaling pathway was discovered in human hepatic cells [174]. However, the effect of melatonin and the S1P signaling pathway in the ovarian follicle activation was not studied yet. Therefore, further studies are needed to discover the efficacy of melatonin in S1P signaling mechanism.

3.2.2. Imatinib

Imatinib is a tyrosine-kinase inhibitor and has been proposed as a fertoprotective adjuvant to prevent dormant follicle loss induced by cisplatin treatment via inhibition of c-Abl kinase [20,65]. Kim et al. demonstrated that cisplatin induces TAp63-dependent expression of c-Abl and TAp73 resulting in activation of BAX expression in the ovary [65]. The activation of BAX is mediated by c-Abl/TAp73/BAX, leading to the death of cisplatin-damaged oocytes during chemotherapy [65]. However, there are several controversial reports that imatinib could not protect dormant oocytes from cisplatin-mediated apoptosis and prevent loss of fertility [175,176]. Because of contradictory studies on imatinib, a further study is required on the protective effect of imatinib against DNA damage in oocytes during chemotherapy. Until now, no studies have been reported on the relationship of melatonin and imatinib in certain tissues and cells. If the precise mechanism of imatinib for fertoprotective effect of ovarian follicle is established correctly, future studies on the association with melatonin will be important as a key to the resolution of ovarian follicle protection conundrum by anti-cancer drugs.

3.2.3. Tamoxifen

Tamoxifen, an antagonist of estrogen receptor, is used as an adjuvant in hormone-sensitive chemotherapy. The administration of tamoxifen significantly decreased chemotherapy-induced follicle loss as well as improved fertility [177]. In addition, it ameliorated doxorubicin-induced DNA fragmentation in mouse oocytes [177], although the detailed mechanisms of tamoxifen-mediated protection during chemotherapy have not been discovered. In the studies linked to melatonin, tamoxifen had been reported as inducing tumor regression with co-treatment of melatonin in

metastatic breast cancer patients [178–180]. In addition, melatonin enhanced the ability of tamoxifen to prevent free radical-induced damages in rat hepatic microsomes [181]. However, Dauchy et al. reported that light-induced melatonin secretion induced intrinsic resistance to tamoxifen therapy [182]. These suggest that further studies are needed to demonstrate the relationship between melatonin and tamoxifen in reproductive organs including the ovary.

3.2.4. GnRH Analog

Several studies demonstrated that the administration of a GnRH analog decreased primordial follicle loss after chemotherapy in an animal model [15,183–185]. A clinical study showed that 281 breast cancer patients who received chemotherapy with a GnRH analog showed significantly attenuated POF [186]. However, two trials with breast cancer patients had conflicting results. One study reported that 69% of GnRH co-administrated patients who received chemotherapy have a normal reproductive cycle [187], and another study reported no difference between GnRH analog administration group and only chemotherapy group [188]. Additional studies reported no significant change in POF incidence after co-administration with a GnRH analog [189–191]. Thus, not only different chemotherapy protocols but also adopting different outcome definitions could explain the difference in results [37]. Studies on the correlation of melatonin with GnRH and melatonin have been reported. Diaz et al. reported that melatonin restored basal pituitary hormone levels and responsiveness to GnRH in acyclic rat model and male testis [192,193]. However, there is no research on the relationship between melatonin and GnRH analog in gonads such as ovary.

3.2.5. Ammonium trichloro (dioxoethylene-*O*,*O*′) tellurate (AS101)

A tellurium compound AS101 was originally developed as an immunomodulatory agent because it stimulates cytokines [194]. However, recent reports demonstrated that AS101 decreases toxicity in several tissues including neurons [195] and testes [196,197]. In particular, AS101 has been reported to protect testes against cyclophosphamide-induced damages and fragmentation of sperm DNA without interfering with chemotherapy effect [196,197]. In female, AS101 also has been shown to suppress follicle loss in cyclophosphamide-activated primordial follicles by inhibiting the PI3K/PTEN/AKT signal pathway during chemotherapy [198,199]. AS101 significantly prevented the burn-out of dormant follicles in chemotherapy-induced mice, and successfully preserved fertility. However, further studies are needed on the side effects of AS101 in clinics and its effect on other fertoprotective agents such as melatonin.

4. Conclusions

Chemotherapy-induced ovarian failure is a highly burdensome gynecological syndrome. It lowers female fertility, induces premature menopause, and causes a variety of hormonal changes in the body. The development of anticancer drugs has greatly increased the survival rate of cancer patients; however, it is important to consider the quality of life as well. Researchers have studied adjuvants that can inhibit or reduce the side effects of various anticancer drugs. In this review, we summarized the chemotherapeutic drugs and adjuvants used for preserving female fertility during chemotherapy. Recently, the efficacy of melatonin as a fertoprotective adjuvant has been reported. Melatonin is a hormone synthesized in the body and it has obvious advantages over other candidates for preserving fertility during chemotherapy. It is relatively higher safer and has less toxicity in various diseases. Consequently, melatonin may be useful in preventing or ameliorating chemotherapy-induced ovarian disorders. This information will provide better understanding for application of melatonin in oncology clinics as a fertoprotective adjuvant for female cancer patients.

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References

1. Waxman, J. Chemotherapy and the adult gonad: A review. *J. R. Soc. Med.* **1983**, *76*, 144–148. [PubMed]
2. Loren, A.W.; Mangu, P.B.; Beck, L.N.; Brennan, L.; Magdalinski, A.J.; Partridge, A.H.; Quinn, G.; Wallace, W.H.; Oktay, K.; American Society of Clinical, Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* **2013**, *31*, 2500–2510. [CrossRef] [PubMed]
3. Peccatori, F.A.; Azim, H.A., Jr.; Orecchia, R.; Hoekstra, H.J.; Pavlidis, N.; Kesic, V.; Pentheroudakis, G.; Group, E.G.W. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2013**, *24*, vi60–vi70. [CrossRef] [PubMed]
4. Paluch-Shimon, S.; Pagani, O.; Partridge, A.H.; Bar-Meir, E.; Fallowfield, L.; Fenlon, D.; Friedman, E.; Gelmon, K.; Gentilini, O.; Geraghty, J.; et al. Second international consensus guidelines for breast cancer in young women (BCY2). *Breast* **2016**, *26*, 87–99. [CrossRef] [PubMed]
5. Mahajan, N. Fertility preservation in female cancer patients: An overview. *J. Hum. Reprod. Sci.* **2015**, *8*, 3–13. [CrossRef] [PubMed]
6. Meirow, D.; Wallace, W.H. Preservation of fertility in patients with cancer. *N. Engl. J. Med.* **2009**, *360*, 2682. [PubMed]
7. Sklar, C.A.; Mertens, A.C.; Mitby, P.; Whitton, J.; Stovall, M.; Kasper, C.; Mulder, J.; Green, D.; Nicholson, H.S.; Yasui, Y.; et al. Premature menopause in survivors of childhood cancer: A report from the childhood cancer survivor study. *J. Natl. Cancer Inst.* **2006**, *98*, 890–896. [CrossRef] [PubMed]
8. Bath, L.E.; Wallace, W.H.; Shaw, M.P.; Fitzpatrick, C.; Anderson, R.A. Depletion of ovarian reserve in young women after treatment for cancer in childhood: Detection by anti-Mullerian hormone, inhibin B and ovarian ultrasound. *Hum. Reprod.* **2003**, *18*, 2368–2374. [CrossRef] [PubMed]
9. Anderson, R.A.; Themmen, A.P.; Al-Qahtani, A.; Groome, N.P.; Cameron, D.A. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum. Reprod.* **2006**, *21*, 2583–2592. [CrossRef] [PubMed]
10. Himelstein-Braw, R.; Peters, H.; Faber, M. Morphological study of the ovaries of leukaemic children. *Br. J. Cancer* **1978**, *38*, 82–87. [CrossRef] [PubMed]
11. Meirow, D.; Nugent, D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum. Reprod. Update* **2001**, *7*, 535–543. [CrossRef] [PubMed]
12. Meirow, D.; Biederman, H.; Anderson, R.A.; Wallace, W.H. Toxicity of chemotherapy and radiation on female reproduction. *Clin. Obstet. Gynecol.* **2010**, *53*, 727–739. [CrossRef] [PubMed]
13. Anderson, R.A.; Wallace, W.H. Antimullerian hormone, the assessment of the ovarian reserve, and the reproductive outcome of the young patient with cancer. *Fertil. Steril.* **2013**, *99*, 1469–1475. [CrossRef] [PubMed]
14. Familiari, G.; Caggiati, A.; Nottola, S.A.; Ermini, M.; di Benedetto, M.R.; Motta, P.M. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. *Hum. Reprod.* **1993**, *8*, 2080–2087. [CrossRef] [PubMed]
15. Ataya, K.; Rao, L.V.; Lawrence, E.; Kimmel, R. Luteinizing hormone-releasing hormone agonist inhibits cyclophosphamide-induced ovarian follicular depletion in rhesus monkeys. *Biol. Reprod.* **1995**, *52*, 365–372. [CrossRef] [PubMed]
16. Meirow, D.; Lewis, H.; Nugent, D.; Epstein, M. Subclinical depletion of primordial follicular reserve in mice treated with cyclophosphamide: Clinical importance and proposed accurate investigative tool. *Hum. Reprod.* **1999**, *14*, 1903–1907. [CrossRef] [PubMed]
17. Maneschi, F.; Benedetti-Panici, P.; Scambia, G.; Salerno, M.G.; D'Agostino, G.; Mancuso, S. Menstrual and hormone patterns in women treated with high-dose cisplatin and bleomycin. *Gynecol. Oncol.* **1994**, *54*, 345–348. [CrossRef] [PubMed]
18. Nozaki, Y.; Furubo, E.; Matsuno, T.; Fukui, R.; Kizawa, K.; Kozaki, T.; Sanzen, T. Collaborative work on evaluation of ovarian toxicity 6. Two- or four-week repeated-dose studies and fertility study of cisplatin in female rats. *J. Toxicol. Sci.* **2009**, *34*, 73–81. [CrossRef]

19. Blommaert, F.A.; Michael, C.; van Dijk-Knijnenburg, H.C.; Schornagel, J.H.; den Engelse, L.; Fichtinger-Schepman, A.M. The formation and persistence of carboplatin-DNA adducts in rats. *Cancer Chemother. Pharmacol.* **1996**, *38*, 273–280. [CrossRef] [PubMed]
20. Gonfloni, S.; di Tella, L.; Caldarola, S.; Cannata, S.M.; Klinger, F.G.; di Bartolomeo, C.; Mattei, M.; Candi, E.; de Felici, M.; Melino, G.; et al. Inhibition of the c-Abl-TAp63 pathway protects mouse oocytes from chemotherapy-induced death. *Nat. Med.* **2009**, *15*, 1179–1185. [CrossRef] [PubMed]
21. Higdon, R.E.; Marchetti, F.; Mailhes, J.B.; Phillips, G.L. The effects of cisplatin on murine metaphase II oocytes. *Gynecol. Oncol.* **1992**, *47*, 348–352. [CrossRef]
22. Mailhes, J.B. Important biological variables that can influence the degree of chemical-induced aneuploidy in mammalian oocyte and zygotes. *Mutat. Res.* **1995**, *339*, 155–176. [CrossRef]
23. Blumenfeld, Z. Chemotherapy and fertility. *Best Pract. Res. Clin. Obs. Gynaecol.* **2012**, *26*, 379–390. [CrossRef] [PubMed]
24. Hortobagyi, G.N.; Buzdar, A.U.; Marcus, C.E.; Smith, T.L. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. *NCI Monogr.* **1986**, *1*, 105–109.
25. Meirow, D. Reproduction post-chemotherapy in young cancer patients. *Mol. Cell. Endocrinol.* **2000**, *169*, 123–131. [CrossRef]
26. Lee, S.J.; Schover, L.R.; Partridge, A.H.; Patrizio, P.; Wallace, W.H.; Hagerty, K.; Beck, L.N.; Brennan, L.V.; Oktay, K.; American Society of Clinical, Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J. Clin. Oncol.* **2006**, *24*, 2917–2931. [CrossRef] [PubMed]
27. Bines, J.; Oleske, D.M.; Cobleigh, M.A. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J. Clin. Oncol.* **1996**, *14*, 1718–1729. [CrossRef] [PubMed]
28. Mol, F.; Mol, B.W.; Ankum, W.M.; van der Veen, F.; Hajenius, P.J. Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: A systematic review and meta-analysis. *Hum. Reprod. Update* **2008**, *14*, 309–319. [CrossRef] [PubMed]
29. Oriol, B.; Barrio, A.; Pacheco, A.; Serna, J.; Zuzuarregui, J.L.; Garcia-Velasco, J.A. Systemic methotrexate to treat ectopic pregnancy does not affect ovarian reserve. *Fertil. Steril.* **2008**, *90*, 1579–1582. [CrossRef] [PubMed]
30. Davis, A.L.; Klitus, M.; Mintzer, D.M. Chemotherapy-induced amenorrhea from adjuvant breast cancer treatment: The effect of the addition of taxanes. *Clin. Breast Cancer* **2005**, *6*, 421–424. [CrossRef] [PubMed]
31. Reh, A.; Oktem, O.; Oktay, K. Impact of breast cancer chemotherapy on ovarian reserve: A prospective observational analysis by menstrual history and ovarian reserve markers. *Fertil. Steril.* **2008**, *90*, 1635–1639. [CrossRef] [PubMed]
32. Han, H.S.; Ro, J.; Lee, K.S.; Nam, B.H.; Seo, J.A.; Lee, D.H.; Lee, H.; Lee, E.S.; Kang, H.S.; Kim, S.W. Analysis of chemotherapy-induced amenorrhea rates by three different anthracycline and taxane containing regimens for early breast cancer. *Breast Cancer Res. Treat.* **2009**, *115*, 335–342. [CrossRef] [PubMed]
33. Abusief, M.E.; Missmer, S.A.; Ginsburg, E.S.; Weeks, J.C.; Partridge, A.H. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. *Cancer* **2010**, *116*, 791–798. [CrossRef] [PubMed]
34. Ganz, P.A.; Land, S.R.; Geyer, C.E., Jr.; Cecchini, R.S.; Costantino, J.P.; Pajon, E.R.; Fehrenbacher, L.; Atkins, J.N.; Polikoff, J.A.; Vogel, V.G.; et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. *J. Clin. Oncol.* **2011**, *29*, 1110–1116. [CrossRef] [PubMed]
35. Petrek, J.A.; Naughton, M.J.; Case, L.D.; Paskett, E.D.; Naftalis, E.Z.; Singletary, S.E.; Sukumvanich, P. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: A prospective study. *J. Clin. Oncol.* **2006**, *24*, 1045–1051. [CrossRef] [PubMed]
36. Higgins, M.J.; Liedke, P.E.; Goss, P.E. Extended adjuvant endocrine therapy in hormone dependent breast cancer: The paradigm of the NCIC-CTG MA.17/BIG 1–97 trial. *Crit. Rev. Oncol. Hematol.* **2013**, *86*, 23–32. [CrossRef] [PubMed]
37. Roness, H.; Kalich-Philosoph, L.; Meirow, D. Prevention of chemotherapy-induced ovarian damage: Possible roles for hormonal and non-hormonal attenuating agents. *Hum. Reprod. Update* **2014**, *20*, 759–774. [CrossRef] [PubMed]

38. Bonadonna, G.; Bonfante, V.; Viviani, S.; di Russo, A.; Villani, F.; Valagussa, P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-term results. *J. Clin. Oncol.* **2004**, *22*, 2835–2841. [CrossRef] [PubMed]
39. Decanter, C.; Morschhauser, F.; Pigny, P.; Lefebvre, C.; Gallo, C.; Dewailly, D. Anti-Mullerian hormone follow-up in young women treated by chemotherapy for lymphoma: Preliminary results. *Reprod. Biomed. Online* **2010**, *20*, 280–285. [CrossRef] [PubMed]
40. Behringer, K.; Mueller, H.; Goergen, H.; Thielen, I.; Eibl, A.D.; Stumpf, V.; Wessels, C.; Wiehlputz, M.; Rosenbrock, J.; Halbsguth, T.; et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J. Clin. Oncol.* **2013**, *31*, 231–239. [CrossRef] [PubMed]
41. Kreuser, E.D.; Felsenberg, D.; Behles, C.; Seibt-Jung, H.; Mielcarek, M.; Diehl, V.; Dahmen, E.; Thiel, E. Long-term gonadal dysfunction and its impact on bone mineralization in patients following COPP/ABVD chemotherapy for Hodgkin's disease. *Ann. Oncol.* **1992**, *3*, 105–110. [CrossRef] [PubMed]
42. Behringer, K.; Breuer, K.; Reineke, T.; May, M.; Nogova, L.; Klimm, B.; Schmitz, T.; Wildt, L.; Diehl, V.; Engert, A.; et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: A report from the German Hodgkin's Lymphoma Study Group. *J. Clin. Oncol.* **2005**, *23*, 7555–7564. [CrossRef] [PubMed]
43. Di Giacomo, M.; Barchi, M.; Baudat, F.; Edelmann, W.; Keeney, S.; Jasin, M. Distinct DNA-damage-dependent and -independent responses drive the loss of oocytes in recombination-defective mouse mutants. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 737–742. [CrossRef] [PubMed]
44. Jurisicova, A.; Lee, H.J.; D'Estaing, S.G.; Tilly, J.; Perez, G.I. Molecular requirements for doxorubicin-mediated death in murine oocytes. *Cell Death Differ.* **2006**, *13*, 1466–1474. [CrossRef] [PubMed]
45. Perez, G.I.; Acton, B.M.; Jurisicova, A.; Perkins, G.A.; White, A.; Brown, J.; Trbovich, A.M.; Kim, M.R.; Fissore, R.; Xu, J.; et al. Genetic variance modifies apoptosis susceptibility in mature oocytes via alterations in DNA repair capacity and mitochondrial ultrastructure. *Cell Death Differ.* **2007**, *14*, 524–533. [CrossRef] [PubMed]
46. Cruz, M.H.; Leal, C.L.; Cruz, J.F.; Tan, D.X.; Reiter, R.J. Essential actions of melatonin in protecting the ovary from oxidative damage. *Theriogenology* **2014**, *82*, 925–932. [CrossRef] [PubMed]
47. Morgan, S.; Anderson, R.A.; Gourley, C.; Wallace, W.H.; Spears, N. How do chemotherapeutic agents damage the ovary? *Hum. Reprod. Update* **2012**, *18*, 525–535. [CrossRef] [PubMed]
48. Carroll, J.; Marangos, P. The DNA damage response in mammalian oocytes. *Front. Genet.* **2013**, *4*, 117. [CrossRef] [PubMed]
49. Oktem, O.; Oktay, K. A novel ovarian xenografting model to characterize the impact of chemotherapy agents on human primordial follicle reserve. *Cancer Res.* **2007**, *67*, 10159–10162. [CrossRef] [PubMed]
50. Picton, H.M.; Harris, S.E.; Muruvi, W.; Chambers, E.L. The in vitro growth and maturation of follicles. *Reproduction* **2008**, *136*, 703–715. [CrossRef] [PubMed]
51. Telfer, E.E.; McLaughlin, M.; Ding, C.; Thong, K.J. A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin. *Hum. Reprod.* **2008**, *23*, 1151–1158. [CrossRef] [PubMed]
52. Jutras, B.L.; Chenail, A.M.; Rowland, C.L.; Carroll, D.; Miller, M.C.; Bykowski, T.; Stevenson, B. Eubacterial SpoVG homologs constitute a new family of site-specific DNA-binding proteins. *PLoS ONE* **2013**, *8*, e66683. [CrossRef] [PubMed]
53. Jang, H.; Lee, O.H.; Lee, Y.; Yoon, H.; Chang, E.M.; Park, M.; Lee, J.W.; Hong, K.; Kim, J.O.; Kim, N.K.; et al. Melatonin prevents cisplatin-induced primordial follicle loss via suppression of PTEN/AKT/FOXO3a pathway activation in the mouse ovary. *J. Pineal Res.* **2016**, *60*, 336–347. [CrossRef] [PubMed]
54. Chang, E.M.; Lim, E.; Yoon, S.; Jeong, K.; Bae, S.; Lee, D.R.; Yoon, T.K.; Choi, Y.; Lee, W.S. Cisplatin induces overactivation of the dormant primordial follicle through PTEN/AKT/FOXO3a pathway which leads to loss of ovarian reserve in mice. *PLoS ONE* **2015**, *10*, e0144245. [CrossRef] [PubMed]
55. Zwain, I.H.; Amato, P. cAMP-induced apoptosis in granulosa cells is associated with up-regulation of P53 and bax and down-regulation of clusterin. *Endocr. Res.* **2001**, *27*, 233–249. [CrossRef] [PubMed]
56. Harris, S.L.; Levine, A.J. The p53 pathway: Positive and negative feedback loops. *Oncogene* **2005**, *24*, 2899–2908. [CrossRef] [PubMed]

57. Depalo, R.; Nappi, L.; Loverro, G.; Bettocchi, S.; Caruso, M.L.; Valentini, A.M.; Selvaggi, L. Evidence of apoptosis in human primordial and primary follicles. *Hum. Reprod.* **2003**, *18*, 2678–2682. [CrossRef] [PubMed]
58. Perez, G.I.; Knudson, C.M.; Leykin, L.; Korsmeyer, S.J.; Tilly, J.L. Apoptosis-associated signaling pathways are required for chemotherapy-mediated female germ cell destruction. *Nat. Med.* **1997**, *3*, 1228–1232. [CrossRef] [PubMed]
59. Kurita, T.; Cunha, G.R.; Robboy, S.J.; Mills, A.A.; Medina, R.T. Differential expression of p63 isoforms in female reproductive organs. *Mech. Dev.* **2005**, *122*, 1043–1055. [CrossRef] [PubMed]
60. Suh, E.K.; Yang, A.; Kettenbach, A.; Bamberger, C.; Michaelis, A.H.; Zhu, Z.; Elvin, J.A.; Bronson, R.T.; Crum, C.P.; McKeon, F. p63 protects the female germ line during meiotic arrest. *Nature* **2006**, *444*, 624–628. [CrossRef] [PubMed]
61. Livera, G.; Petre-Lazar, B.; Guerquin, M.J.; Trautmann, E.; Coffigny, H.; Habert, R. p63 null mutation protects mouse oocytes from radio-induced apoptosis. *Reproduction* **2008**, *135*, 3–12. [CrossRef] [PubMed]
62. Kerr, J.B.; Hutt, K.J.; Michalak, E.M.; Cook, M.; Vandenberg, C.J.; Liew, S.H.; Bouillet, P.; Mills, A.; Scott, C.L.; Findlay, J.K.; et al. DNA damage-induced primordial follicle oocyte apoptosis and loss of fertility require TAp63-mediated induction of Puma and Noxa. *Mol. Cell* **2012**, *48*, 343–352. [CrossRef] [PubMed]
63. Kharbanda, S.; Yuan, Z.M.; Weichselbaum, R.; Kufe, D. Determination of cell fate by c-Abl activation in the response to DNA damage. *Oncogene* **1998**, *17*, 3309–3318. [CrossRef] [PubMed]
64. Yoshida, K.; Miki, Y. Enabling death by the Abl tyrosine kinase: Mechanisms for nuclear shuttling of c-Abl in response to DNA damage. *Cell Cycle* **2005**, *4*, 777–779. [CrossRef] [PubMed]
65. Kim, S.Y.; Cordeiro, M.H.; Serna, V.A.; Ebbert, K.; Butler, L.M.; Sinha, S.; Mills, A.A.; Woodruff, T.K.; Kurita, T. Rescue of platinum-damaged oocytes from programmed cell death through inactivation of the p53 family signaling network. *Cell Death Differ.* **2013**, *20*, 987–997. [CrossRef] [PubMed]
66. Bolcun-Filas, E.; Rinaldi, V.D.; White, M.E.; Schimenti, J.C. Reversal of female infertility by Chk2 ablation reveals the oocyte DNA damage checkpoint pathway. *Science* **2014**, *343*, 533–536. [CrossRef] [PubMed]
67. Reddy, P.; Liu, L.; Adhikari, D.; Jagarlamudi, K.; Rajareddy, S.; Shen, Y.; Du, C.; Tang, W.; Hamalainen, T.; Peng, S.L.; et al. Oocyte-specific deletion of PTEN causes premature activation of the primordial follicle pool. *Science* **2008**, *319*, 611–613. [CrossRef] [PubMed]
68. Jagarlamudi, K.; Liu, L.; Adhikari, D.; Reddy, P.; Idahl, A.; Ottander, U.; Lundin, E.; Liu, K. Oocyte-specific deletion of PTEN in mice reveals a stage-specific function of PTEN/PI3K signaling in oocytes in controlling follicular activation. *PLoS ONE* **2009**, *4*, e6186. [CrossRef] [PubMed]
69. Nakahata, S.; Ichikawa, T.; Maneesaay, P.; Saito, Y.; Nagai, K.; Tamura, T.; Manachai, N.; Yamakawa, N.; Hamasaki, M.; Kitabayashi, I.; et al. Loss of NDRG2 expression activates PI3K-AKT signalling via PTEN phosphorylation in ATLL and other cancers. *Nat. Commun.* **2014**, *5*, 3393. [CrossRef] [PubMed]
70. Silva, A.; Yunes, J.A.; Cardoso, B.A.; Martins, L.R.; Jotta, P.Y.; Abecasis, M.; Nowill, A.E.; Leslie, N.R.; Cardoso, A.A.; Barata, J.T. PTEN posttranslational inactivation and hyperactivation of the PI3K/Akt pathway sustain primary T cell leukemia viability. *J. Clin. Investig.* **2008**, *118*, 3762–3774. [CrossRef] [PubMed]
71. Li, J.; Kawamura, K.; Cheng, Y.; Liu, S.; Klein, C.; Liu, S.; Duan, E.K.; Hsueh, A.J. Activation of dormant ovarian follicles to generate mature eggs. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 10280–10284. [CrossRef] [PubMed]
72. Kawamura, K.; Cheng, Y.; Suzuki, N.; Deguchi, M.; Sato, Y.; Takae, S.; Ho, C.H.; Kawamura, N.; Tamura, M.; Hashimoto, S.; et al. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 17474–17479. [CrossRef] [PubMed]
73. Zheng, W.; Nagaraju, G.; Liu, Z.; Liu, K. Functional roles of the phosphatidylinositol 3-kinases (PI3Ks) signaling in the mammalian ovary. *Mol. Cell. Endocrinol.* **2012**, *356*, 24–30. [CrossRef] [PubMed]
74. Groszer, M.; Erickson, R.; Scripture-Adams, D.D.; Lesche, R.; Trumpp, A.; Zack, J.A.; Kornblum, H.I.; Liu, X.; Wu, H. Negative regulation of neural stem/progenitor cell proliferation by the PTEN tumor suppressor gene in vivo. *Science* **2001**, *294*, 2186–2189. [CrossRef] [PubMed]
75. Al-Khouri, A.M.; Ma, Y.; Togo, S.H.; Williams, S.; Mustelin, T. Cooperative phosphorylation of the tumor suppressor phosphatase and tensin homologue (PTEN) by casein kinases and glycogen synthase kinase 3β. *J. Biol. Chem.* **2005**, *280*, 35195–35202. [CrossRef] [PubMed]

76. Ning, K.; Miller, L.C.; Laidlaw, H.A.; Burgess, L.A.; Perera, N.M.; Downes, C.P.; Leslie, N.R.; Ashford, M.L. A novel leptin signalling pathway via PTEN inhibition in hypothalamic cell lines and pancreatic β-cells. *EMBO J.* **2006**, *25*, 2377–2387. [CrossRef] [PubMed]
77. Maccario, H.; Perera, N.M.; Davidson, L.; Downes, C.P.; Leslie, N.R. PTEN is destabilized by phosphorylation on Thr366. *Biochem. J.* **2007**, *405*, 439–444. [CrossRef] [PubMed]
78. Manning, B.D.; Tee, A.R.; Logsdon, M.N.; Blenis, J.; Cantley, L.C. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/Akt pathway. *Mol. Cell* **2002**, *10*, 151–162. [CrossRef]
79. Shioi, T.; McMullen, J.R.; Kang, P.M.; Douglas, P.S.; Obata, T.; Franke, T.F.; Cantley, L.C.; Izumo, S. Akt/protein kinase B promotes organ growth in transgenic mice. *Mol. Cell. Biol.* **2002**, *22*, 2799–2809. [CrossRef] [PubMed]
80. Gonzalez, E.; McGraw, T.E. The Akt kinases: Isoform specificity in metabolism and cancer. *Cell Cycle* **2009**, *8*, 2502–2508. [CrossRef] [PubMed]
81. Roness, H.; Gavish, Z.; Cohen, Y.; Meirow, D. Ovarian follicle burnout: A universal phenomenon? *Cell Cycle* **2013**, *12*, 3245–3246. [CrossRef] [PubMed]
82. Castrillon, D.H.; Miao, L.; Kollipara, R.; Horner, J.W.; DePinho, R.A. Suppression of ovarian follicle activation in mice by the transcription factor Foxo3a. *Science* **2003**, *301*, 215–218. [CrossRef] [PubMed]
83. Dijkers, P.F.; Medema, R.H.; Pals, C.; Banerji, L.; Thomas, N.S.; Lam, E.W.; Burgering, B.M.; Raaijmakers, J.A.; Lammers, J.W.; Koenderman, L.; et al. Forkhead transcription factor FKHR-L1 modulates cytokine-dependent transcriptional regulation of p27(KIP1). *Mol. Cell. Biol.* **2000**, *20*, 9138–9148. [CrossRef] [PubMed]
84. Sherr, C.J.; Roberts, J.M. CDK inhibitors: Positive and negative regulators of G1-phase progression. *Genes Dev.* **1999**, *13*, 1501–1512. [CrossRef] [PubMed]
85. Rajareddy, S.; Reddy, P.; Du, C.; Liu, L.; Jagarlamudi, K.; Tang, W.; Shen, Y.; Berthet, C.; Peng, S.L.; Kaldis, P.; et al. p27kip1 (cyclin-dependent kinase inhibitor 1B) controls ovarian development by suppressing follicle endowment and activation and promoting follicle atresia in mice. *Mol. Endocrinol.* **2007**, *21*, 2189–2202. [CrossRef] [PubMed]
86. Stehle, J.; Reuss, S.; Riemann, R.; Seidel, A.; Vollrath, L. The role of arginine-vasopressin for pineal melatonin synthesis in the rat: Involvement of vasopressinergic receptors. *Neurosci. Lett.* **1991**, *123*, 131–134. [CrossRef]
87. Venegas, C.; Garcia, J.A.; Escames, G.; Ortiz, F.; Lopez, A.; Doerrier, C.; Garcia-Corzo, L.; Lopez, L.C.; Reiter, R.J.; Acuna-Castroviejo, D. Extrapineal melatonin: Analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **2012**, *52*, 217–227. [CrossRef] [PubMed]
88. Reiter, R.J.; Rosales-Corral, S.A.; Manchester, L.C.; Tan, D.X. Peripheral reproductive organ health and melatonin: Ready for prime time. *Int. J. Mol. Sci.* **2013**, *14*, 7231–7272. [CrossRef] [PubMed]
89. Tan, D.X.; Manchester, L.C.; Liu, X.; Rosales-Corral, S.A.; Acuna-Castroviejo, D.; Reiter, R.J. Mitochondria and chloroplasts as the original sites of melatonin synthesis: A hypothesis related to melatonin's primary function and evolution in eukaryotes. *J. Pineal Res.* **2013**, *54*, 127–138. [CrossRef] [PubMed]
90. Reiter, R.J.; Tan, D.X.; Tamura, H.; Cruz, M.H.; Fuentes-Broto, L. Clinical relevance of melatonin in ovarian and placental physiology: A review. *Gynecol. Endocrinol.* **2014**, *30*, 83–89. [CrossRef] [PubMed]
91. Reiter, R.J.; Tan, D.X.; Korkmaz, A.; Rosales-Corral, S.A. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. *Hum. Reprod. Update* **2014**, *20*, 293–307. [CrossRef] [PubMed]
92. Hardeland, R.; Tan, D.X.; Reiter, R.J. Kynuramines, metabolites of melatonin and other indoles: The resurrection of an almost forgotten class of biogenic amines. *J. Pineal Res.* **2009**, *47*, 109–126. [CrossRef] [PubMed]
93. Tan, D.X.; Manchester, L.C.; Terron, M.P.; Flores, L.J.; Reiter, R.J. One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J. Pineal Res.* **2007**, *42*, 28–42. [CrossRef] [PubMed]
94. Zhang, H.M.; Zhang, Y. Melatonin: A well-documented antioxidant with conditional pro-oxidant actions. *J. Pineal Res.* **2014**, *57*, 131–146. [CrossRef] [PubMed]
95. Galano, A.; Medina, M.E.; Tan, D.X.; Reiter, R.J. Melatonin and its metabolites as copper chelating agents and their role in inhibiting oxidative stress: A physicochemical analysis. *J. Pineal Res.* **2015**, *58*, 107–116. [CrossRef] [PubMed]
96. Reiter, R.J. Oxidative damage in the central nervous system: Protection by melatonin. *Prog. Neurobiol.* **1998**, *56*, 359–384. [CrossRef]

97. Reiter, R.J.; Tan, D.X.; Allegra, M. Melatonin: Reducing molecular pathology and dysfunction due to free radicals and associated reactants. *Neuro Endocrinol. Lett.* **2002**, *23*, 3–8. [CrossRef] [PubMed]
98. Reiter, R.J.; Tan, D.X.; Rosales-Corral, S.; Manchester, L.C. The universal nature, unequal distribution and antioxidant functions of melatonin and its derivatives. *Mini Rev. Med. Chem.* **2013**, *13*, 373–384. [CrossRef] [PubMed]
99. Acuna-Castroviejo, D.; Escames, G.; Venegas, C.; Diaz-Casado, M.E.; Lima-Cabello, E.; Lopez, L.C.; Rosales-Corral, S.; Tan, D.X.; Reiter, R.J. Extrapineal melatonin: Sources, regulation, and potential functions. *Cell. Mol. Life Sci.* **2014**, *71*, 2997–3025. [CrossRef] [PubMed]
100. Parlakpinar, H.; Sahna, E.; Ozer, M.K.; Ozugurlu, F.; Vardi, N.; Acet, A. Physiological and pharmacological concentrations of melatonin protect against cisplatin-induced acute renal injury. *J. Pineal Res.* **2002**, *33*, 161–166. [CrossRef] [PubMed]
101. Kilic, U.; Kilic, E.; Tuzcu, Z.; Tuzcu, M.; Ozercan, I.H.; Yilmaz, O.; Sahin, F.; Sahin, K. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of Nrf-2/HO-1 pathway. *Nutr. Metab.* **2013**, *10*, 7. [CrossRef] [PubMed]
102. Reiter, R.J.; Tan, D.X.; Pappolla, M.A. Melatonin relieves the neural oxidative burden that contributes to dementias. *Ann. N. Y Acad. Sci.* **2004**, *1035*, 179–196. [CrossRef] [PubMed]
103. Zhao, H.; Wu, Q.Q.; Cao, L.F.; Qing, H.Y.; Zhang, C.; Chen, Y.H.; Wang, H.; Liu, R.Y.; Xu, D.X. Melatonin inhibits endoplasmic reticulum stress and epithelial-mesenchymal transition during bleomycin-induced pulmonary fibrosis in mice. *PLoS ONE* **2014**, *9*, e97266. [CrossRef] [PubMed]
104. He, C.; Wang, J.; Li, Y.; Zhu, K.; Xu, Z.; Song, Y.; Song, Y.; Liu, G. Melatonin-related genes expressed in the mouse uterus during early gestation promote embryo implantation. *J. Pineal Res.* **2015**, *58*, 300–309. [CrossRef] [PubMed]
105. Dair, E.L.; Simoes, R.S.; Simoes, M.J.; Romeu, L.R.; Oliveira-Filho, R.M.; Haidar, M.A.; Baracat, E.C.; Soares, J.M. Effects of melatonin on the endometrial morphology and embryo implantation in rats. *Fertil. Steril.* **2008**, *89*, 1299–1305. [CrossRef] [PubMed]
106. Atessahin, A.; Sahna, E.; Turk, G.; Ceribasi, A.O.; Yilmaz, S.; Yuce, A.; Bulmus, O. Chemoprotective effect of melatonin against cisplatin-induced testicular toxicity in rats. *J. Pineal Res.* **2006**, *41*, 21–27. [CrossRef] [PubMed]
107. Galano, A.; Tan, D.X.; Reiter, R.J. Melatonin as a natural ally against oxidative stress: A physicochemical examination. *J. Pineal Res.* **2011**, *51*, 1–16. [CrossRef] [PubMed]
108. Reiter, R.J.; Richardson, B.A.; Johnson, L.Y.; Ferguson, B.N.; Dinh, D.T. Pineal melatonin rhythm: Reduction in aging Syrian hamsters. *Science* **1980**, *210*, 1372–1373. [CrossRef] [PubMed]
109. Reiter, R.J.; Craft, C.M.; Johnson, J.E., Jr.; King, T.S.; Richardson, B.A.; Vaughan, G.M.; Vaughan, M.K. Age-associated reduction in nocturnal pineal melatonin levels in female rats. *Endocrinology* **1981**, *109*, 1295–1297. [CrossRef] [PubMed]
110. Coto-Montes, A.; Boga, J.A.; Tan, D.X.; Reiter, R.J. Melatonin as a potential agent in the treatment of sarcopenia. *Int. J. Mol. Sci.* **2016**, *17*, 1771. [CrossRef] [PubMed]
111. Bubenik, G.A.; Konturek, S.J. Melatonin and aging: Prospects for human treatment. *J. Physiol. Pharmacol.* **2011**, *62*, 13–19. [PubMed]
112. Hill, S.M.; Cheng, C.; Yuan, L.; Mao, L.; Jockers, R.; Dauchy, B.; Blask, D.E. Age-related decline in melatonin and its MT1 receptor are associated with decreased sensitivity to melatonin and enhanced mammary tumor growth. *Curr. Aging Sci.* **2013**, *6*, 125–133. [CrossRef] [PubMed]
113. Caballero, B.; Vega-Naredo, I.; Sierra, V.; Huidobro-Fernandez, C.; Soria-Valles, C.; de Gonzalo-Calvo, D.; Tolivia, D.; Gutierrez-Cuesta, J.; Pallas, M.; Camins, A.; et al. Favorable effects of a prolonged treatment with melatonin on the level of oxidative damage and neurodegeneration in senescence-accelerated mice. *J. Pineal Res.* **2008**, *45*, 302–311. [CrossRef] [PubMed]
114. Sanchez-Barcelo, E.J.; Mediavilla, M.D.; Tan, D.X.; Reiter, R.J. Clinical uses of melatonin: Evaluation of human trials. *Curr. Med. Chem.* **2010**, *17*, 2070–2095. [CrossRef] [PubMed]
115. Mockova, K.; Mnichova, M.; Kubatka, P.; Bojkova, B.; Ahlers, I.; Ahlersova, E. Mammary carcinogenesis induced in Wistar:han rats by the combination of ionizing radiation and dimethylbenz(a)anthracene: Prevention with melatonin. *Neoplasma* **2000**, *47*, 227–229. [PubMed]

116. Majidinia, M.; Sadeghpour, A.; Mehrzadi, S.; Reiter, R.J.; Khatami, N.; Yousefi, B. Melatonin: A pleiotropic molecule that modulates DNA damage response and repair pathways. *J. Pineal Res.* **2017**, 1–16. [CrossRef] [PubMed]
117. Khan, S.; Adhikari, J.S.; Rizvi, M.A.; Chaudhury, N.K. Radioprotective potential of melatonin against ^{60}Co γ-ray-induced testicular injury in male C57BL/6 mice. *J. Biomed. Sci.* **2015**, *22*, 61. [CrossRef] [PubMed]
118. Cos, S.; Mediavilla, M.D.; Fernandez, R.; Gonzalez-Lamuno, D.; Sanchez-Barcelo, E.J. Does melatonin induce apoptosis in MCF-7 human breast cancer cells in vitro? *J. Pineal Res.* **2002**, *32*, 90–96. [CrossRef] [PubMed]
119. Martin-Renedo, J.; Mauriz, J.L.; Jorquera, F.; Ruiz-Andres, O.; Gonzalez, P.; Gonzalez-Gallego, J. Melatonin induces cell cycle arrest and apoptosis in hepatocarcinoma HepG2 cell line. *J. Pineal Res.* **2008**, *45*, 532–540. [CrossRef] [PubMed]
120. Mediavilla, M.D.; Cos, S.; Sanchez-Barcelo, E.J. Melatonin increases p53 and p21WAF1 expression in MCF-7 human breast cancer cells in vitro. *Life Sci.* **1999**, *65*, 415–420. [CrossRef]
121. Proietti, S.; Cucina, A.; Dobrowolny, G.; D'Anselmi, F.; Dinicola, S.; Masiello, M.G.; Pasqualato, A.; Palombo, A.; Morini, V.; Reiter, R.J.; et al. Melatonin down-regulates *MDM2* gene expression and enhances p53 acetylation in MCF-7 cells. *J. Pineal Res.* **2014**, *57*, 120–129. [CrossRef] [PubMed]
122. Santoro, R.; Marani, M.; Blandino, G.; Muti, P.; Strano, S. Melatonin triggers p53Ser phosphorylation and prevents DNA damage accumulation. *Oncogene* **2012**, *31*, 2931–2942. [CrossRef] [PubMed]
123. Santoro, R.; Mori, F.; Marani, M.; Grasso, G.; Cambria, M.A.; Blandino, G.; Muti, P.; Strano, S. Blockage of melatonin receptors impairs p53-mediated prevention of DNA damage accumulation. *Carcinogenesis* **2013**, *34*, 1051–1061. [CrossRef] [PubMed]
124. Reppert, S.M.; Weaver, D.R.; Ebisawa, T.; Mahle, C.D.; Kolakowski, L.F., Jr. Cloning of a melatonin-related receptor from human pituitary. *FEBS Lett.* **1996**, *386*, 219–224. [CrossRef]
125. Overington, J.P.; Al-Lazikani, B.; Hopkins, A.L. How many drug targets are there? *Nat. Rev. Drug Discov.* **2006**, *5*, 993–996. [CrossRef] [PubMed]
126. Kilic, E.; Kilic, U.; Reiter, R.J.; Bassetti, C.L.; Hermann, D.M. Prophylactic use of melatonin protects against focal cerebral ischemia in mice: Role of endothelin converting enzyme-1. *J. Pineal Res.* **2004**, *37*, 247–251. [CrossRef] [PubMed]
127. Cerezo, A.B.; Hornedo-Ortega, R.; Alvarez-Fernandez, M.A.; Troncoso, A.M.; Garcia-Parrilla, M.C. Inhibition of VEGF-Induced VEGFR-2 activation and HUVEC migration by melatonin and other bioactive indolic compounds. *Nutrients* **2017**, *9*, 249. [CrossRef] [PubMed]
128. Lissoni, P.; Rovelli, F.; Malugani, F.; Bucovec, R.; Conti, A.; Maestroni, G.J. Anti-angiogenic activity of melatonin in advanced cancer patients. *Neurol. Endocrinol. Lett.* **2001**, *22*, 45–47. [PubMed]
129. Jardim-Perassi, B.V.; Arbab, A.S.; Ferreira, L.C.; Borin, T.F.; Varma, N.R.; Iskander, A.S.; Shankar, A.; Ali, M.M.; de Campos Zuccari, D.A. Effect of melatonin on tumor growth and angiogenesis in xenograft model of breast cancer. *PLoS ONE* **2014**, *9*, e85311. [CrossRef] [PubMed]
130. Castle-Miller, J.; Bates, D.O.; Tortonese, D.J. Mechanisms regulating angiogenesis underlie seasonal control of pituitary function. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 2514–2523. [CrossRef] [PubMed]
131. Miller, S.C.; Pandi-Perumal, S.R.; Esquifino, A.I.; Cardinali, D.P.; Maestroni, G.J. The role of melatonin in immuno-enhancement: Potential application in cancer. *Int. J. Exp. Pathol.* **2006**, *87*, 81–87. [CrossRef] [PubMed]
132. Konakchieva, R.; Kyurkchiev, S.; Kehayov, I.; Taushanova, P.; Kanchev, L. Selective effect of methoxyindoles on the lymphocyte proliferation and melatonin binding to activated human lymphoid cells. *J. Neuroimmunol.* **1995**, *63*, 125–132. [CrossRef]
133. Pioli, C.; Caroleo, M.C.; Nistico, G.; Doria, G. Melatonin increases antigen presentation and amplifies specific and non specific signals for T-cell proliferation. *Int. J. Immunopharmacol.* **1993**, *15*, 463–468. [CrossRef]
134. Raghavendra, V.; Singh, V.; Shaji, A.V.; Vohra, H.; Kulkarni, S.K.; Agrewala, J.N. Melatonin provides signal 3 to unprimed CD4+ T cells but failed to stimulate LPS primed B cells. *Clin. Exp. Immunol.* **2001**, *124*, 414–422. [CrossRef] [PubMed]
135. Drazen, D.L.; Bilu, D.; Bilbo, S.D.; Nelson, R.J. Melatonin enhancement of splenocyte proliferation is attenuated by luzindole, a melatonin receptor antagonist. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2001**, *280*, 1476–1482.
136. Wajs, E.; Kutoh, E.; Gupta, D. Melatonin affects proopiomelanocortin gene expression in the immune organs of the rat. *Eur. J. Endocrinol.* **1995**, *133*, 754–760. [CrossRef] [PubMed]

137. Garcia-Maurino, S.; Gonzalez-Haba, M.G.; Calvo, J.R.; Rafii-El-Idrissi, M.; Sanchez-Margalet, V.; Goberna, R.; Guerrero, J.M. Melatonin enhances IL-2, IL-6, and IFN-γ production by human circulating CD4+ cells: A possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes. *J. Immunol.* **1997**, *159*, 574–581. [PubMed]
138. Liu, F.; Ng, T.B.; Fung, M.C. Pineal indoles stimulate the gene expression of immunomodulating cytokines. *J. Neural Transm.* **2001**, *108*, 397–405. [CrossRef] [PubMed]
139. Currier, N.L.; Sun, L.Z.; Miller, S.C. Exogenous melatonin: Quantitative enhancement in vivo of cells mediating non-specific immunity. *J. Neuroimmunol.* **2000**, *104*, 101–108. [CrossRef]
140. Currier, N.L.; Miller, S.C. Echinacea purpurea and melatonin augment natural-killer cells in leukemic mice and prolong life span. *J. Altern. Complement. Med.* **2001**, *7*, 241–251. [CrossRef] [PubMed]
141. Yoo, Y.M.; Jang, S.K.; Kim, G.H.; Park, J.Y.; Joo, S.S. Pharmacological advantages of melatonin in immunosenescence by improving activity of T lymphocytes. *J. Biomed. Res.* **2016**, *30*, 314–321. [PubMed]
142. Agarwal, A.; Gupta, S.; Sharma, R.K. Role of oxidative stress in female reproduction. *Reprod. Biol. Endocrinol.* **2005**, *3*, 28. [CrossRef] [PubMed]
143. Pham-Huy, L.A.; He, H.; Pham-Huy, C. Free radicals, antioxidants in disease and health. *Int. J. Biomed. Sci.* **2008**, *4*, 89–96. [PubMed]
144. Ruder, E.H.; Hartman, T.J.; Blumberg, J.; Goldman, M.B. Oxidative stress and antioxidants: Exposure and impact on female fertility. *Hum. Reprod. Update* **2008**, *14*, 345–357. [CrossRef] [PubMed]
145. Choi, Y.; Rajkovic, A. Genetics of early mammalian folliculogenesis. *Cell. Mol. Life Sci.* **2006**, *63*, 579–590. [CrossRef] [PubMed]
146. Lim, E.J.; Choi, Y. Transcription factors in the maintenance and survival of primordial follicles. *Clin. Exp. Reprod. Med.* **2012**, *39*, 127–131. [CrossRef] [PubMed]
147. Tamura, H.; Takasaki, A.; Miwa, I.; Taniguchi, K.; Maekawa, R.; Asada, H.; Taketani, T.; Matsuoka, A.; Yamagata, Y.; Shimamura, K.; et al. Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. *J. Pineal Res.* **2008**, *44*, 280–287. [CrossRef] [PubMed]
148. Tamura, H.; Nakamura, Y.; Korkmaz, A.; Manchester, L.C.; Tan, D.X.; Sugino, N.; Reiter, R.J. Melatonin and the ovary: Physiological and pathophysiological implications. *Fertil. Steril.* **2009**, *92*, 328–343. [CrossRef] [PubMed]
149. Tamura, H.; Takasaki, A.; Taketani, T.; Tanabe, M.; Kizuka, F.; Lee, L.; Tamura, I.; Maekawa, R.; Aasada, H.; Yamagata, Y.; et al. The role of melatonin as an antioxidant in the follicle. *J. Ovarian Res.* **2012**, *5*, 5. [CrossRef] [PubMed]
150. Kim, M.K.; Park, E.A.; Kim, H.J.; Choi, W.Y.; Cho, J.H.; Lee, W.S.; Cha, K.Y.; Kim, Y.S.; Lee, D.R.; Yoon, T.K. Does supplementation of in vitro culture medium with melatonin improve IVF outcome in PCOS? *Reprod. Biomed. Online* **2013**, *26*, 22–29. [CrossRef] [PubMed]
151. Ma, M.; Chen, X.Y.; Li, B.; Li, X.T. Melatonin protects premature ovarian insufficiency induced by tripterygium glycosides: Role of SIRT1. *Am. J. Transl. Res.* **2017**, *9*, 1580–1602. [PubMed]
152. Chattoraj, A.; Seth, M.; Maitra, S.K. Localization and dynamics of Mel(1a) melatonin receptor in the ovary of carp Catla catla in relation to serum melatonin levels. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* **2009**, *152*, 327–333. [CrossRef] [PubMed]
153. Jablonska, K.; Pula, B.; Zemla, A.; Kobierzycki, C.; Kedzia, W.; Nowak-Markwitz, E.; Spaczynski, M.; Zabel, M.; Podhorska-Okolow, M.; Dziegiel, P. Expression of the MT1 melatonin receptor in ovarian cancer cells. *Int. J. Mol. Sci.* **2014**, *15*, 23074–23089. [CrossRef] [PubMed]
154. Soares, J.M., Jr.; Masana, M.I.; Ersahin, C.; Dubocovich, M.L. Functional melatonin receptors in rat ovaries at various stages of the estrous cycle. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 694–702. [CrossRef] [PubMed]
155. Reiter, R.J.; Tan, D.X.; Sainz, R.M.; Mayo, J.C.; Lopez-Burillo, S. Melatonin: Reducing the toxicity and increasing the efficacy of drugs. *J. Pharm Pharmacol.* **2002**, *54*, 1299–1321. [CrossRef] [PubMed]
156. Mills, E.; Wu, P.; Seely, D.; Guyatt, G. Melatonin in the treatment of cancer: A systematic review of randomized controlled trials and meta-analysis. *J. Pineal Res.* **2005**, *39*, 360–366. [CrossRef] [PubMed]
157. Casado-Zapico, S.; Rodriguez-Blanco, J.; Garcia-Santos, G.; Martin, V.; Sanchez-Sanchez, A.M.; Antolin, I.; Rodriguez, C. Synergistic antitumor effect of melatonin with several chemotherapeutic drugs on human Ewing sarcoma cancer cells: Potentiation of the extrinsic apoptotic pathway. *J. Pineal Res.* **2010**, *48*, 72–80. [CrossRef] [PubMed]

158. Tan, D.X.; Manchester, L.C.; Reiter, R.J.; Plummer, B.F.; Hardies, L.J.; Weintraub, S.T.; Shepherd, A.M. A novel melatonin metabolite, cyclic 3-hydroxymelatonin: A biomarker of in vivo hydroxyl radical generation. *Biochem. Biophys. Res. Commun.* **1998**, *253*, 614–620. [CrossRef] [PubMed]
159. Pariente, R.; Pariente, J.A.; Rodriguez, A.B.; Espino, J. Melatonin sensitizes human cervical cancer HeLa cells to cisplatin-induced cytotoxicity and apoptosis: Effects on oxidative stress and DNA fragmentation. *J. Pineal Res.* **2016**, *60*, 55–64. [CrossRef] [PubMed]
160. Lee, C.J.; Do, B.R.; Lee, Y.H.; Park, J.H.; Kim, S.J.; Kim, J.K.; Roh, S.I.; Yoon, Y.D.; Yoon, H.S. Ovarian expression of melatonin Mel(1a) receptor mRNA during mouse development. *Mol. Reprod. Dev.* **2001**, *59*, 126–132. [CrossRef] [PubMed]
161. Niles, L.P.; Wang, J.; Shen, L.; Lobb, D.K.; Younglai, E.V. Melatonin receptor mRNA expression in human granulosa cells. *Mol. Cell. Endocrinol.* **1999**, *156*, 107–110. [CrossRef]
162. Wang, S.J.; Liu, W.J.; Wu, C.J.; Ma, F.H.; Ahmad, S.; Liu, B.R.; Han, L.; Jiang, X.P.; Zhang, S.J.; Yang, L.G. Melatonin suppresses apoptosis and stimulates progesterone production by bovine granulosa cells via its receptors (MT1 and MT2). *Theriogenology* **2012**, *78*, 1517–1526. [CrossRef] [PubMed]
163. Woo, M.M.; Tai, C.J.; Kang, S.K.; Nathwani, P.S.; Pang, S.F.; Leung, P.C. Direct action of melatonin in human granulosa-luteal cells. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 4789–4797. [CrossRef] [PubMed]
164. Kong, P.J.; Byun, J.S.; Lim, S.Y.; Lee, J.J.; Hong, S.J.; Kwon, K.J.; Kim, S.S. Melatonin induces Akt phosphorylation through melatonin receptor- and PI3K-dependent pathways in primary astrocytes. *Korean J. Physiol. Pharmacol.* **2008**, *12*, 37–41. [CrossRef] [PubMed]
165. Kilic, U.; Caglayan, A.B.; Beker, M.C.; Gunal, M.Y.; Caglayan, B.; Yalcin, E.; Kelestemur, T.; Gundogdu, R.Z.; Yulug, B.; Yilmaz, B.; et al. Particular phosphorylation of PI3K/Akt on Thr308 via PDK-1 and PTEN mediates melatonin's neuroprotective activity after focal cerebral ischemia in mice. *Redox Biol.* **2017**, *12*, 657–665. [CrossRef] [PubMed]
166. Nakamura, Y.; Tamura, H.; Takayama, H.; Kato, H. Increased endogenous level of melatonin in preovulatory human follicles does not directly influence progesterone production. *Fertil. Steril.* **2003**, *80*, 1012–1016. [CrossRef]
167. Shi, J.M.; Tian, X.Z.; Zhou, G.B.; Wang, L.; Gao, C.; Zhu, S.E.; Zeng, S.M.; Tian, J.H.; Liu, G.S. Melatonin exists in porcine follicular fluid and improves in vitro maturation and parthenogenetic development of porcine oocytes. *J. Pineal Res.* **2009**, *47*, 318–323. [CrossRef] [PubMed]
168. Morita, Y.; Perez, G.I.; Paris, F.; Miranda, S.R.; Ehleiter, D.; Haimovitz-Friedman, A.; Fuks, Z.; Xie, Z.; Reed, J.C.; Schuchman, E.H.; et al. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. *Nat. Med.* **2000**, *6*, 1109–1114. [PubMed]
169. Hancke, K.; Strauch, O.; Kissel, C.; Gobel, H.; Schafer, W.; Denschlag, D. Sphingosine 1-phosphate protects ovaries from chemotherapy-induced damage in vivo. *Fertil. Steril.* **2007**, *87*, 172–177. [CrossRef] [PubMed]
170. Li, F.; Turan, V.; Lierman, S.; Cuvelier, C.; de Sutter, P.; Oktay, K. Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death. *Hum. Reprod.* **2014**, *29*, 107–113. [CrossRef] [PubMed]
171. Kaya, H.; Desdicioglu, R.; Sezik, M.; Ulukaya, E.; Ozkaya, O.; Yilmaztepe, A.; Demirci, M. Does sphingosine-1-phosphate have a protective effect on cyclophosphamide- and irradiation-induced ovarian damage in the rat model? *Fertil. Steril.* **2008**, *89*, 732–735. [CrossRef] [PubMed]
172. Crespo, I.; San-Miguel, B.; Sanchez, D.I.; Gonzalez-Fernandez, B.; Alvarez, M.; Gonzalez-Gallego, J.; Tunon, M.J. Melatonin inhibits the sphingosine kinase 1/sphingosine-1-phosphate signaling pathway in rabbits with fulminant hepatitis of viral origin. *J. Pineal Res.* **2016**, *61*, 168–176. [CrossRef] [PubMed]
173. Sanchez, D.I.; Gonzalez-Fernandez, B.; San-Miguel, B.; de Urbina, J.O.; Crespo, I.; Gonzalez-Gallego, J.; Tunon, M.J. Melatonin prevents deregulation of the sphingosine kinase/sphingosine 1-phosphate signaling pathway in a mouse model of diethylnitrosamine-induced hepatocellular carcinoma. *J. Pineal Res.* **2017**, *62*, 1–15. [CrossRef] [PubMed]
174. Gonzalez-Fernandez, B.; Sanchez, D.I.; Crespo, I.; San-Miguel, B.; Alvarez, M.; Tunon, M.J.; Gonzalez-Gallego, J. Inhibition of the SphK1/S1P signaling pathway by melatonin in mice with liver fibrosis and human hepatic stellate cells. *BioFactors* **2017**, *43*, 272–282. [CrossRef] [PubMed]
175. Kerr, J.B.; Hutt, K.J.; Cook, M.; Speed, T.P.; Strasser, A.; Findlay, J.K.; Scott, C.L. Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. *Nat. Med.* **2012**, *18*, 1170–1172. [CrossRef] [PubMed]

176. Maiani, E.; di Bartolomeo, C.; Klinger, F.G.; Cannata, S.M.; Bernardini, S.; Chateauvieux, S.; Mack, F.; Mattei, M.; de Felici, M.; Diederich, M.; et al. Reply to: Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. *Nat. Med.* **2012**, *18*, 1172–1174. [CrossRef] [PubMed]
177. Ting, A.Y.; Petroff, B.K. Tamoxifen decreases ovarian follicular loss from experimental toxicant DMBA and chemotherapy agents cyclophosphamide and doxorubicin in the rat. *J. Assisted Reprod. Genet.* **2010**, *27*, 591–597. [CrossRef] [PubMed]
178. Lissoni, P.; Barni, S.; Meregalli, S.; Fossati, V.; Cazzaniga, M.; Esposti, D.; Tancini, G. Modulation of cancer endocrine therapy by melatonin: A phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone. *Br. J. Cancer* **1995**, *71*, 854–856. [CrossRef] [PubMed]
179. Lissoni, P.; Ardizzoia, A.; Barni, S.; Paolorossi, F.; Tancini, G.; Meregalli, S.; Esposti, D.; Zubelewicz, B.; Braczowski, R. A randomized study of tamoxifen alone versus tamoxifen plus melatonin in estrogen receptor-negative heavily pretreated metastatic breast-cancer patients. *Oncol. Rep.* **1995**, *2*, 871–873. [CrossRef] [PubMed]
180. Lissoni, P.; Paolorossi, F.; Tancini, G.; Ardizzoia, A.; Barni, S.; Brivio, F.; Maestroni, G.J.; Chilelli, M. A phase II study of tamoxifen plus melatonin in metastatic solid tumour patients. *Br. J. Cancer* **1996**, *74*, 1466–1468. [CrossRef] [PubMed]
181. Garcia, J.J.; Reiter, R.J.; Ortiz, G.G.; Oh, C.S.; Tang, L.; Yu, B.P.; Escames, G. Melatonin enhances tamoxifen's ability to prevent the reduction in microsomal membrane fluidity induced by lipid peroxidation. *J. Membr. Biol.* **1998**, *162*, 59–65. [CrossRef] [PubMed]
182. Dauchy, R.T.; Xiang, S.; Mao, L.; Brimer, S.; Wren, M.A.; Yuan, L.; Anbalagan, M.; Hauch, A.; Frasch, T.; Rowan, B.G.; et al. Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer Res.* **2014**, *74*, 4099–4110. [CrossRef] [PubMed]
183. Meirow, D.; Assad, G.; Dor, J.; Rabinovici, J. The GnRH antagonist cetrorelix reduces cyclophosphamide-induced ovarian follicular destruction in mice. *Hum. Reprod.* **2004**, *19*, 1294–1299. [CrossRef] [PubMed]
184. Kishk, E.A.; Mohammed Ali, M.H. Effect of a gonadotropin-releasing hormone analogue on cyclophosphamide-induced ovarian toxicity in adult mice. *Arch. Gynecol. Obstet.* **2013**, *287*, 1023–1029. [CrossRef] [PubMed]
185. Li, X.; Kang, X.; Deng, Q.; Cai, J.; Wang, Z. Combination of a GnRH agonist with an antagonist prevents flare-up effects and protects primordial ovarian follicles in the rat ovary from cisplatin-induced toxicity: A controlled experimental animal study. *Reprod. Biol. Endocrinol.* **2013**, *11*, 16. [CrossRef] [PubMed]
186. Del Mastro, L.; Boni, L.; Michelotti, A.; Gamucci, T.; Olmeo, N.; Gori, S.; Giordano, M.; Garrone, O.; Pronzato, P.; Bighin, C.; et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: A randomized trial. *JAMA* **2011**, *306*, 269–276. [CrossRef] [PubMed]
187. Badawy, A.; Elnashar, A.; El-Ashry, M.; Shahat, M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: Prospective randomized study. *Fertil. Steril.* **2009**, *91*, 694–697. [CrossRef] [PubMed]
188. Elgindy, E.A.; El-Haieg, D.O.; Khorshid, O.M.; Ismail, E.I.; Abdelgawad, M.; Sallam, H.N.; Abou-Setta, A.M. Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: A randomized controlled trial. *Obstet. Gynecol.* **2013**, *121*, 78–86. [CrossRef] [PubMed]
189. Gerber, B.; von Minckwitz, G.; Stehle, H.; Reimer, T.; Felberbaum, R.; Maass, N.; Fischer, D.; Sommer, H.L.; Conrad, B.; Ortmann, O.; et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: The GBG 37 ZORO study. *J. Clin. Oncol.* **2011**, *29*, 2334–2341. [CrossRef] [PubMed]
190. Sverrisdottir, A.; Nystedt, M.; Johansson, H.; Fornander, T. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: Results from a randomized trial. *Breast Cancer Res. Treat.* **2009**, *117*, 561–567. [CrossRef] [PubMed]
191. Munster, P.N.; Moore, A.P.; Ismail-Khan, R.; Cox, C.E.; Lacevic, M.; Gross-King, M.; Xu, P.; Carter, W.B.; Minton, S.E. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J. Clin. Oncol.* **2012**, *30*, 533–538. [CrossRef] [PubMed]

192. Diaz, E.; Pazo, D.; Esquifino, A.I.; Diaz, B. Effects of ageing and exogenous melatonin on pituitary responsiveness to GnRH in rats. *J. Reprod. Fertil.* **2000**, *119*, 151–156. [CrossRef] [PubMed]
193. Diaz, E.; Castrillon, P.; Esquifino, A.; Diaz, B. Effect of prenatal melatonin on the gonadotropin and prolactin response to the feedback effect of testosterone in male offspring. *J. Steroid Biochem. Mol. Biol.* **2000**, *72*, 61–69. [CrossRef]
194. Montero, R.; Gonsebatt, M.E.; Gerson, R.; Rojas, E.; Herrera, L.A.; Ostrosky-Wegman, P. AS-101: A modulator of in vitro T-cell proliferation. *Anti-Cancer Drugs* **1993**, *4*, 351–354. [CrossRef] [PubMed]
195. Makarovsky, D.; Kalechman, Y.; Sonino, T.; Freidkin, I.; Teitz, S.; Albeck, M.; Weil, M.; Geffen-Aricha, R.; Yadid, G.; Sredni, B. Tellurium compound AS101 induces PC12 differentiation and rescues the neurons from apoptotic death. *Ann. N. Y Acad. Sci.* **2003**, *1010*, 659–666. [CrossRef] [PubMed]
196. Carmely, A.; Meirow, D.; Peretz, A.; Albeck, M.; Bartoov, B.; Sredni, B. Protective effect of the immunomodulator AS101 against cyclophosphamide-induced testicular damage in mice. *Hum. Reprod.* **2009**, *24*, 1322–1329. [CrossRef] [PubMed]
197. Maman, E.; Prokopis, K.; Levron, J.; Carmely, A.; Dor, J.; Meirow, D. Does controlled ovarian stimulation prior to chemotherapy increase primordial follicle loss and diminish ovarian reserve? An animal study. *Hum. Reprod.* **2009**, *24*, 206–210. [CrossRef] [PubMed]
198. Kalich-Philosoph, L.; Roness, H.; Carmely, A.; Fishel-Bartal, M.; Ligumsky, H.; Paglin, S.; Wolf, I.; Kanety, H.; Sredni, B.; Meirow, D. Cyclophosphamide triggers follicle activation and "burnout"; AS101 prevents follicle loss and preserves fertility. *Sci. Transl. Med.* **2013**, *5*, 185. [CrossRef] [PubMed]
199. Hayun, M.; Naor, Y.; Weil, M.; Albeck, M.; Peled, A.; Don, J.; Haran-Ghera, N.; Sredni, B. The immunomodulator AS101 induces growth arrest and apoptosis in multiple myeloma: Association with the Akt/survivin pathway. *Biochem. Pharmacol.* **2006**, *72*, 1423–1431. [CrossRef] [PubMed]