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Title: Chemotherapy and female fertility

Titre: Effets de la chimiothérapie sur la fertilité féminine

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Abstract

Chemotherapy to treat cancer is usually responsible for early ovarian follicle depletion. Ovarian damage induced by cancer treatments frequently results in infertility in surviving patients of childbearing age. Several fertility preservation techniques have been developed. Nowadays, oocyte or embryo cryopreservation with or without ovarian stimulation and cryopreservation of the ovarian cortex are the most commonly used. However, these methods may be difficult to implement in some situations, and subsequent use of the cryopreserved germ cells remains uncertain, with no guarantee of pregnancy. Improved knowledge of the molecular mechanisms and signaling pathways involved in chemotherapy-induced ovarian damage is therefore necessary, to develop new strategies for fertility preservation. The effects of various chemotherapies have been studied in animal models or *in vitro* on ovarian cultures, suggesting various mechanisms of gonadotoxicity. Today the challenge is to develop molecules and techniques to limit the negative impact of chemotherapy on the ovaries, using experimental models, especially in animals. In this review, the various theories concerning ovarian damage induced by chemotherapy will be reviewed and emerging approaches for ovarian protection will be explained.

Résumé

Les chimiothérapies utilisées pour traiter les différents types de cancers peuvent être responsables d'une déplétion précoce de la réserve ovarienne qui peut conduire à une infertilité chez les jeunes femmes en âge de procréer. Afin de palier à cet effet secondaire, plusieurs techniques de préservation de la fertilité féminine ont été développée comme la cryopréservation d'ovocytes ou d'embryons avec ou sans stimulation hormonale préalable

ou la cryopréservation de tissu ovarien. Cependant dans certaines situations cliniques, ces différentes méthodes peuvent être difficiles à réaliser. Par ailleurs l'utilisation ultérieure des gamètes cryoconservés reste incertaine et ne présente pas une garantie de grossesse ultérieure. Une meilleure connaissance des mécanismes moléculaires et des voies de signalisation impliquées dans la toxicité ovarienne induites par la chimiothérapie est donc nécessaire pour développer de nouvelles stratégies de préservation de la fertilité. Les effets de diverses chimiothérapies ont été étudiés dans des modèles animaux ou *in vitro* sur des cultures d'ovaire et ont permis de proposer différents mécanismes de gonadotoxicité. Aujourd'hui, le défi est de développer des molécules et des techniques pour limiter l'impact négatif de la chimiothérapie sur les ovaires en utilisant des modèles expérimentaux, en particulier chez l'animal. Dans cette revue, les différentes théories concernant les dommages ovariens induits par la chimiothérapie seront énumérées et les approches émergentes pour la protection des ovaires seront expliquées.

Keywords: fertility preservation; primordial follicles; ovarian reserve; chemotherapy-induced ovarian damage

Mots clefs : préservation de la fertilité ; follicule primordial ; réserve ovarienne ; altération de la réserve ovarienne chimio-induite

Introduction

Over the last decade, early diagnosis of cancer and advances in oncological technologies have led to enhanced survival rates in children and young women of childbearing age (1). However, cancer treatments such as chemotherapy, radiotherapy or surgery may impair ovarian reserve by reducing the follicle stockpile, which can lead to damaged ovarian function and loss of fertility, whereas post-cure fertility is a major concern for cancer survivors (2–4). A few options are available to preserve gametes in case of infertility after recovery from cancer: oocyte or embryo cryopreservation following ovarian stimulation (OS) or *in vitro* maturation (IVM) or ovarian tissue cryopreservation (OTC) (3). Nevertheless, the application of these techniques may be limited by patient's age at treatment, pubertal status, disease and emergency treatment initiation. Emerging fertility techniques are under development: stem cell-based therapy using induced pluripotent stem cells (iPSCs) or ovarian stem cells (5). Recently, germline-competent iPSCs were derived from adult mouse granulosa cells by chemical treatment, and generated functional oocytes and fertile mice (6). Activation and maturation of primordial follicles is another technique, and would be revolutionary (7). Lastly, advances in bioengineering and improvement in 3D-printing have led to several experiments to develop 3D-printed ovarian functional scaffolds. Recently, in animal models, both endocrine and reproductive ovarian functions were restored using an artificial ovary, with reported pregnancies (8).

One of the major challenges in fertility preservation (FP) is to find new approaches to protect the ovaries from chemotherapy-induced damage or to restore reproductive and/or endocrine ovarian function (5). Several studies have suggested various mechanisms to explain ovarian damage induced by each chemotherapy agent, using different experimental models.

In this review, after a brief reminder on the regulation of ovarian reserve, we present the various theories of ovarian damage induced by chemotherapy, and discuss emerging approaches for ovarian protection.

1-What is the ovarian reserve and how it is regulated?

The ovarian follicle reserve in mammals is constituted by primordial follicles (PMFs). This follicle stockpile is established early in life then declines regularly throughout the female reproductive period. Each PMF can remain quiescent for years. At any time, it can be activated and enter the growth process or become atretic (9). Activated PMFs develop through primary and secondary stages before reaching the antral stage by acquiring an antral cavity (Figure 1). Most antral follicles then undergo apoptotic degeneration. After puberty, only a few grow further to reach the preovulatory stage.

The regulation of female reproductive and endocrine functions depends on the stock of quiescent PMFs and the balance between PMF activation and repression mechanisms. In humans, PMF activation starts during fetal life, whereas in other species such as rodents it begins a few days after birth. PMF quiescence is maintained by several molecules: phosphatase and tensin homolog deleted on chromosome 10 (Pten), tuberous sclerosis complexes 1–2 (Tsc1–Tsc2), forkhead box protein O3A (Foxo3A), p27, anti-Müllerian hormone (AMH), and forkhead box L2 (FoxL2) (6). Follicular activation is regulated by other signaling pathways, such as the phosphatidylinositol-3-kinase (PI3K) signaling pathway. The transcription factor FoxO3A, mainly expressed in the oocytes of resting follicles, acts downstream of the PI3K signaling pathway (10). PMF survival and apoptosis are regulated by the expression of antiapoptotic and proapoptotic factors, of which B-cell lymphoma 2 protein (Bcl-2) and Bcl-2-associated X protein (BAX) likely play a critical role. Therefore, coordination

between suppression and activation associated to maintaining dormancy processes are required to preserve the PMF stockpile. Any disorder in these mechanisms can lead to premature ovarian reserve depletion (11).

2-How does chemotherapy damage the ovary?

The gonadal toxicity of chemotherapy is characterized by both temporary and permanent toxicity effects, directly on the ovaries and sometimes on the follicles. From the beginning of treatment, chemotherapy induces DNA damage in the granulosa cells and/or oocytes of growing follicles, leading to follicle apoptosis, resulting in temporary amenorrhea. Some chemotherapies can induce loss of PMFs, resulting in diminished ovarian reserve (DOR) and, in the most severe cases, primary ovarian insufficiency (POI). The extent of ovarian damage depends upon several factors, of which the most important are the type of drug, dose and protocol (7). Chemotherapeutic agents can be divided into 5 categories: alkylating agents, showing the highest potential gonadotoxicity, antitumor antibiotics, platinum-based drugs, alkaloids, and antimetabolites (Table 1).

The mechanisms involved in the gonadotoxicity of these molecules were explored in various experimental models: analysis of histological female ovary cross-sections after chemotherapy, animal models treated with injection, xenograft models, or cell cultures in the presence of active metabolites of chemical agents; however, the mechanisms are not well established (12). Both PMFs and granulosa cells of growing follicles are sensitive to various chemotherapy agents. Oocyte assessment depends on granulosa cell assessment. Thus, follicles, at any stage, can be damaged by all types of chemotherapy agents (5).

Several hypotheses have been proposed, and could coexist. Firstly, chemotherapy drugs can induce DNA damage and subsequent apoptosis in granulosa cells and oocytes. It has also

been suggested that these drugs could trigger indirect PMF depletion by over-recruitment: the so-called “burn-out effect”. Also, chemotherapy drugs may damage ovarian blood vessels, leading to follicle ischemia. Increasing knowledge of the possible mechanisms involved in chemotherapy-induced ovarian damage will facilitate the development of new therapies (13).

3-What are the available options for FP?

Several FP techniques are currently available, including oocyte or embryo vitrification following controlled OS or after IVM, and OTC. Metaphase II oocyte vitrification after OS is the most well-established method in women without an urgent need to initiate cancer treatment (3,4); however, it takes an average of 2 weeks and can be associated with hyperestradiolemia, although specific protocols have been developed to reduce the time required for stimulation (random start) and to avoid the increase in serum estradiol levels or its effects (14). When chemotherapy is urgent or OS is contraindicated, IVM can be proposed, even if it is considered as an innovative technique (3). Thus, IVM could be chosen for FP in patients of childbearing age before starting chemotherapy. Regardless of the technique, the number of frozen oocytes is one of the main keys to success (15,16). Due to the unpredictable immature oocyte recovery rate and the lower oocyte maturation rate with IVM, this technique leads to a lower number of metaphase II oocytes vitrified compared to OS (15,17).

Oocyte cryopreservation after OS cannot be conducted in prepubertal girls. OTC is the only option available for prepubertal girls undergoing gonadotoxic treatment, and may also be a means of preserving reproductive potential in patients who must urgently undergo aggressive chemotherapy and/or radiotherapy. Ovarian tissue is obtained surgically by

laparoscopy, then transferred to the laboratory for cryopreservation. Later, orthotopic or heterotopic auto-transplantation of cryopreserved ovarian tissue is performed, with the purpose of restoring ovarian reproductive and endocrine functions. Transplantation of cryopreserved ovarian tissue is the only option presently able to restore endocrine ovarian function in cancer survivors; however, the risk of reintroducing cancer should be considered, and depends on the type of cancer.

Thus, the FP options should be discussed with oncologists, reproductive specialists and patients, and depend on several factors: patient characteristics (age, ovarian parameters, etc.), the time available before chemotherapy initiation, and the type of malignancy.

4- What about gonadotropin-releasing hormone analogs?

One of the suggested strategies for FP is the use of gonadotropin-releasing hormone analogs (GnRHa). However, the action mechanism of the ovarian protective effect of GnRHa in chemotherapy is unclear (18). It is suggested that GnRHa downregulation of the hypothalamic–pituitary–ovarian axis before and during chemotherapy decreases gonadotropin levels and prevents PMF activation, so that the number of growing follicles, which are more vulnerable to chemotherapy, decreases. In addition, GnRHa may limit accumulation of chemotherapy drugs in the ovary by reducing blood supply to the ovary. The efficacy of GnRHa in ovarian protection against chemotherapy side-effects is unsure, with conflicting results being reported. POI incidence, chemotherapy-induced amenorrhea, menses recovery and pregnancy rates when GnRHa is administered during chemotherapy have not been well evaluated (19).

Given the current state of evidence and safety data, the European Society of Human Reproduction and Embryology (ESHRE) suggested that GnRHa should not be routinely

proposed instead of cryopreservation techniques as an option for ovarian function protection and/or FP without discussion of the attendant uncertainties. However, GnRH α could be associated to other FP techniques (3).

5-What are the fertoprotective agents developed to deal with gonadotoxicity?

Increasing knowledge of the molecular mechanisms and signaling pathways of chemotherapeutic agents reveals potential targets for protective agents to reduce or prevent ovarian damage. As PMF overactivation and apoptosis play important roles in chemotherapy-associated ovarian damage, anti-activation and anti-apoptotic molecules, called fertoprotective agents, have been proposed as candidates to prevent chemotherapy-induced ovarian toxicity. **Figure 1** summarizes the main fertoprotective agents that have been evaluated in mouse models.

- **Sphingolipids:** Sphingosine-1-phosphate (S1P) is a membrane sphingolipid involved in physiological processes of ovarian follicle apoptosis. Several studies demonstrated that S1P is able to protect against chemotherapy-induced ovarian damage and prevent PMF apoptosis after cyclophosphamide or doxorubicin treatment in mouse models and a human ovarian xenograft model (9,12,20,21). Another sphingolipid, ceramide 1 phosphate (C1P), was also found to be a potential ovarian protective agent: ovarian administration reduced cyclophosphamide-induced follicle depletion, through inhibition of follicle apoptosis and improvement of the stromal vasculature (22). One of the major limitations of these treatments is that they must be administered either directly into the ovaries or continuously. However, a long-acting oral form of an S1P analog was recently developed, making these molecules potentially appropriate for use in humans (23).

- **Anti-Müllerian hormone (AMH)** is a glycoprotein hormone expressed by granulosa cells from the primary stage of development until selection for dominance. Because AMH has been shown to limit activation of primordial follicles in *in vivo* and *in vitro* mouse models (24–26), it was suggested in several recent studies that it could be an effective means of limiting chemotherapy-induced gonadotoxicity (27–29). This hypothesis was supported by the expression of the specific AMH receptor, AmhrII, in mouse follicles following the primordial stage (25,27). Recombinant AMH has also been used to improve the results of ovarian tissue cryopreservation, as manipulation of the ovarian cortex after removal induced severe loss of primordial follicles, possibly via a burn-out effect (30,31). Consequently, *in vivo* or *in vitro* AMH treatment could protect the follicle stockpile under these conditions and improve the fertility preservation technique (32).

- **Imatinib** is a competitive tyrosine kinase inhibitor usually used in hematological cancer. It is involved in the apoptotic pathway induced by DNA damage. Based on its role as a c-Abl kinase inhibitor, imatinib was evaluated as a fertoprotective agent against cisplatin-induced PMF loss *in vivo* and *in vitro*. However, these results were contradicted by other studies suggesting that imatinib does not protect PMFs from cisplatin-induced apoptosis and does not preserve fertility (33,34). Thus, additional studies are needed to evaluate whether imatinib could be a new treatment to limit cisplatin gonadotoxicity. Moreover, as imatinib interferes with the apoptotic pathway, it will be crucial to be sure that imatinib does not interfere with the antitumor activity of cisplatin.

- **Anti-DNA damage molecules** have also been proposed as fertoprotective agents, as chemotherapy can induce DNA damage such as double-stranded breaks (DSB). DSBs are one of the most severe DNA lesions, leading to activation of DNA repair pathways allowing cell survival (35). When the repair pathways are not sufficiently activated, DNA damage induces

cell death by apoptosis. These mechanisms are particularly complex in the ovaries, and differ according to the type of chemotherapy molecule. A recent extensive review discussed induction and repair of DNA damage in the ovaries (35). The efficiency of the DNA repair pathway is a key determinant of cell survival following spontaneous or chemotherapy-induced DNA damage. Thus, several studies tried to develop molecules to induce DNA repair in order to preserve follicle survival and limit follicle depletion (5,36,37).

- **AS101 [ammonium trichloro(dioxoethylene-*o,o'*)tellurate]** is an immunomodulatory compound that modulates the PI3K–Pten–Akt pathway (38). AS101 was found to reduce cyclophosphamide-induced follicle depletion in a mouse model (26). Moreover, no increase in fetal malformation was observed in mice previously treated with AS101, indicating the safety of this treatment for offspring in this model.

- **Melatonin** is a hormone secreted by the pineal gland and is commonly used in connection with various biological processes, especially for insomnia treatment. Recently, it was suggested that melatonin could be used as a fertoprotective agent during chemotherapy (39–41). Interestingly, melatonin receptors are present on oocytes and granulosa cells in various species, including humans (42,43). The molecular mechanisms involved in the gonadoprotective effect of melatonin could be mediated by inhibiting follicle recruitment through activation of the PI3K–Akt–FoxO3a signaling pathway (41).

- **mTOR inhibitors:** mTOR is a serine/threonine kinase involved in several critical processes such as cell growth, proliferation, autophagy and cell survival (44). In animal models, mTOR stimulators increase PMF activation while mTOR inhibitors block primordial-to-primary follicle transition (45,46). Recent studies therefore used mTOR inhibitors to preserve ovarian reserve from cyclophosphamide-induced follicle depletion in mice (47–49).

- **Resveratrol (3,5,4'-trihydroxy-trans-stilbene)** is a natural antioxidant with various biological properties, including anti-inflammatory, anticancer and anti-aging effects. A protective effect against chemotherapy-induced oxidative stress was recently demonstrated (50–52). As a reminder, oxidative stress in ovaries induces PMF apoptosis. Given evidence of anticancer effects, resveratrol could be used as an adjuvant in combination with cancer therapy to protect ovarian function (5).

- **miRNAs** are small non-coding RNAs of about 21–22 nucleotides in length which are involved in post-transcriptional gene regulation. Recently, several studies showed that miRNA may be a new fertoprotective strategy during gonadotoxic therapy by preventing PMF atresia and granulosa cell apoptosis. Different miRNAs are being studied in experimental models. However, several technical difficulties are encountered: miRNA stability and ability to avoid phagocytosis or cleavage by endonucleases before reaching the target (53–56).

Conclusion

Increasing knowledge of mechanisms implicated in chemotherapy-induced ovarian damage facilitates the development of new therapies that aim at protecting the follicular reserve. If the protective role of these new therapies is confirmed in humans, they could be used in combination with the currently available fertility preservation techniques and administered regardless of age, pathology or treatment. Moreover, they would also prevent hormonal deficiencies and their consequences (e.g., pubertal delay, osteoporosis). Finally, these treatments may be of particular interest to women with impaired ovarian reserve for whom no fertility preservation method can be proposed.

Class of agent	Infertility risk	Examples	Ovarian Damage
Alkylating agent	High risk	Cyclophosphamide Bisulfan Melphalan	PMF activation PMF apoptosis Granulosa cell apoptosis Follicular atresia
Platinum-based compounds	Intermediate risk	Cisplatin Carboplatin	PMF apoptosis PMF activation Follicular apoptosis Granulosa cell apoptosis
Anthracyclin antibiotics	Low risk / intermediate risk	Doxorubicin Epirubicin Bleomycin	PMF apoptosis Follicular atresia Oxidative stress
Vinca alkaloids	Low risk	Vincristine Vinblastine	PMF apoptosis
Antimetabolites	Low risk	Methotrexate 5-fluorouracil	Follicular atresia

Table 1 : Chemotherapy agents that can lead to ovarian damage (5,57–60).

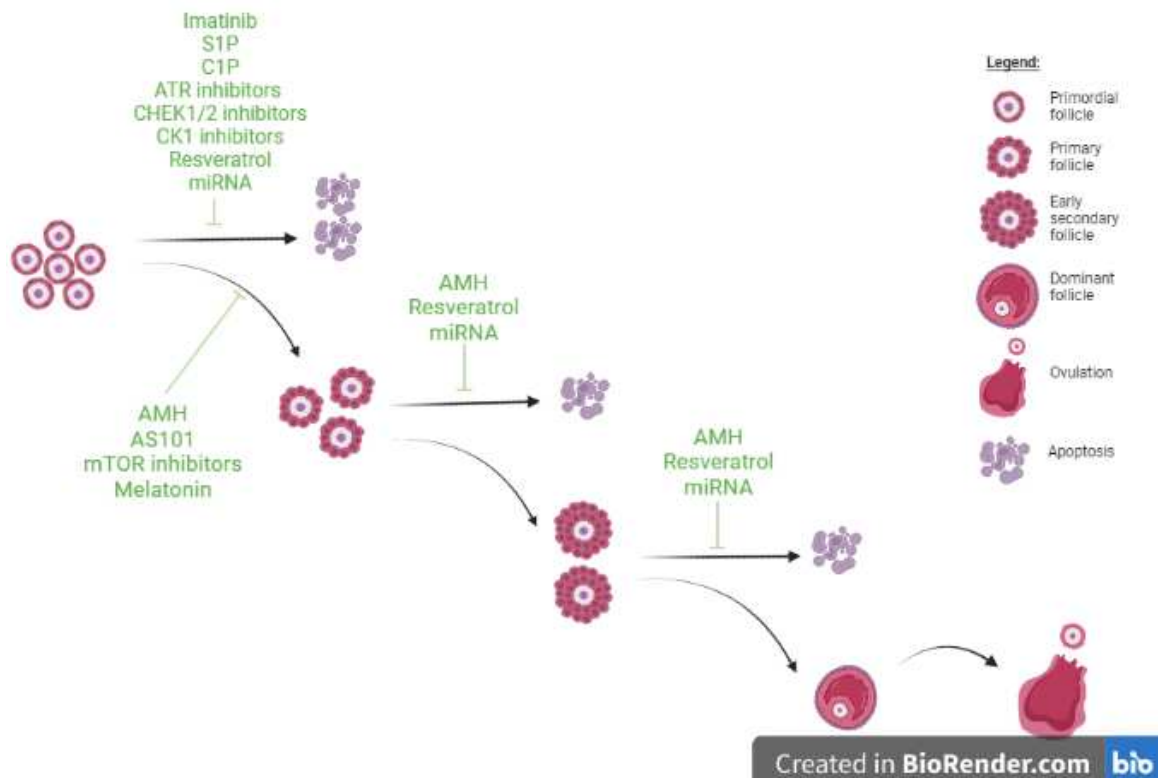


Figure 1: Main molecules evaluated in experimental models to limit chemotherapy-induced follicle depletion.

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