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Research progress on the effect of chemotherapy drugs on ovarian function in breast cancer

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Abstract: In women with reproductive potential, ovarian dysfunction caused by chemotherapy for breast cancer has far-reaching effects. Ovarian insufficiency can manifest as amenorrhea, menstrual disorders, hot flashes and night sweats, impaired fertility in the short term, and increased cardiovascular risk, reduced bone density, cognitive impairment in the long term. The occurrence of ovarian insufficiency due to chemotherapy is closely related to the type of drug, the number of chemotherapy sessions, the dose of chemotherapy, and the age of the patient. There are many drugs for protecting ovarian function, but in clinical practice, gonadotropin-releasing hormone analogues (GnRHa) are still the mainstay. Other ovarian protection drugs generally lack clinical trial data, and their safety and impact on chemotherapy efficacy need further research.

Keywords: Breast cancer; Ovarian reserve function; Adjuvant chemotherapy; Cyclophosphamide; Gonadotropin-releasing hormone agonists; Platinum; Anthracycline; Taxane; Fertility preservation; Goserelin; Tamoxifen

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The onset age of breast cancer tends to be younger in recent years, and nearly 10% of breast cancer cases occur in women under 45 years old [1]. In the existing literature, the pregnancy rate of women with a history of breast cancer is 40%-60% lower than that of the general population [2]. The improvement in China's economic level and quality of life, changes in women's attitudes towards marriage and childbirth, and the increasing proportion of women marrying and having children at a later age have led to a situation where many women of reproductive age have not yet given birth when diagnosed with breast cancer. With the improvement of survival rates, the reproductive and reproductive issues of young female cancer patients have received increasing attention.

There are three systematic treatment modes: chemotherapy, endocrine therapy and targeted therapy [3]. While chemotherapy drugs have been successful in improving overall survival (OS) and extending progression-free survival (PFS) in breast cancer patients, they also have an impact on various organs and tissues throughout the body. For women, among these chemotherapy side effects, premature ovarian insufficiency (POI) may have a negative impact on their overall health for life, leading to infertility and long or short cycle of menstruation. Preserving ovarian function is highly correlated with many premenopausal women, regardless of their age and desire to conceive. Consistent with the previous guidelines, "young women" are defined as women less than 40 years old at the time of diagnosis of breast cancer. Compared with breast cancer in elderly women, young women with breast cancer are more likely to have tumors with aggressive phenotypes [4]. The types of chemotherapy drugs, the number of chemotherapy cycles, and the dosage given may be more intensive compared to older women, but age should be considered in conjunction with other factors and should not be the sole determinant for refusing or recommending treatment. In young premenopausal patients, if the patient is desired, fertility preservation techniques should be discussed before starting any systematic treatment [5]. Ovarian suppression obtained by using gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy is currently recommended as a strategy to preserve the ovarian function of premenopausal breast cancer patients, but cannot be used as an independent fertility preservation technique [6]. However, the current guidelines do not mention whether ovarian protective agents can completely or maximally protect ovarian function. This review aims to summarize the impact of common chemotherapy drugs for breast cancer on ovarian function, with the hope of selecting chemotherapy regimens that are more suitable for young breast cancer patients of reproductive age in the future, through the choice of chemotherapy drugs and their combinations, without compromising the quality of patient survival.

1 Effect of breast cancer chemotherapy drugs on ovarian function

1.1 Pathophysiology

There are multiple mechanisms regarding the potential pathophysiology of gonadal toxicity induced by chemotherapy, including ovarian tissue ischemia, follicle apoptosis, follicle death, follicle destruction, etc. Ovarian tissue ischemia may be caused by vasoconstriction or inhibition of angiogenesis caused by chemotherapy drugs [7]. Follicular apoptosis directly originates from DNA cross-linking/embedding or inhibition of protein synthesis through DNA methylation. Follicular death may also arise from disruption of the follicular cycle, as inhibition of microtubule assembly can cause follicles to arrest in the mid-stage [8]. The destruction of follicles leads to the loss of anti-Müllerian hormone (AMH), weakened inhibition of the primordial follicle pool, and overact the primordial follicles. Cytotoxic chemotherapy drugs deplete ovarian storage and impair ovarian function and fertility.

1.2 Molecular mechanism

In mammals, ovarian reserves are established early in life and steadily declines throughout the reproductive years. Chemotherapy can have adverse effects on ovarian reserve function [5,9]. Chemotherapy induced amenorrhea may be transient, and menstruation may recover after treatment. However, the restoration of menstrual cycles does not necessarily indicate the recovery of ovarian function. Oocytes and granulosa cells are susceptible to the effects of chemotherapy drugs [10]. Each drug may have different mechanisms of action on cancer cells, resulting in cell cycle arrest. The excessive growth of primordial follicles, through direct and indirect cytotoxic effects, leads to premature and irreversible depletion of growing follicles, known as "cytotoxicity". There are also mechanisms of gonadal toxicity such as activation of the PI3K/PTEN/Akt pathway and follicular fatigue [11], as well as ovarian atrophy with fibrosis [12]. Meanwhile, the latest research indicates that chemotherapy drugs induce iron death in ovarian cells by increasing the generation of reactive oxygen species, excessive lipid peroxidation, and mitochondrial dysfunction, leading to ovarian cell death [13]. The known gonadotoxic chemotherapy drugs in breast cancer chemotherapy drugs include cyclophosphamide, anthracycline, paclitaxel and platinum, which are commonly used in current treatment schemes.

1.2.1 Cyclophosphamide alkylating agents

Cyclophosphamide itself is a prodrug that is metabolized by cytochrome P450 in the liver to form 4-hydroxycyclophosphamide, which is then converted to phosphoramide mustard and acrolein. Phosphoramide mustard is the main active metabolite that induces DNA cross-linking, leading to the formation of adducts and thus preventing DNA replication. Phosphoramide mustard can also affect mitochondria, leading to a decrease in transmembrane potential and cytoplasmic cytochrome c accumulation [14]. Alkylating agents are the main cause of increased oxidative stress in the ovaries and can even attack the reserve follicle pool, resulting in DNA fragmentation regardless of cell division. Though there is a dose-dependent effect, follicular destruction can also occur at lower doses [10]. Subsequently, the accumulated DNA strand breaks activated the pro apoptotic pathway within the cell, leading to apoptosis of affected ovarian follicles [8]. Cyclophosphamide can also damage ovarian function by consuming primordial follicles [15].

1.2.2 Platinum

Platinum is composed of heavy metals and serves as a DNA cross-linking agent, interfering with DNA repair mechanisms, preventing cell division, causing DNA damage, and inducing cell apoptosis [14]. By forming interstrand/intrastrand DNA adducts, it disrupts cellular transcription and replication, resulting in DNA damage. The accumulation of ABL and TAp63-alpha proteins in oocytes leads to oocyte death [16]. Platinum is generally considered to have moderate ovarian toxicity. In addition to covalently binding to DNA, platinum can also bind to nuclear and cytoplasmic proteins, which may have adverse toxic effects on patients [17]. These mechanisms may increase its gonadal toxicity.

1.2.3 Anthracycline

Anthracycline is effective components of curative chemotherapy for breast cancer, mainly by inhibiting the role of topoisomerase-II and DNA, preventing its replication and transcription [18]. Under high levels of DNA damage, upregulation of P53 protein induces cell apoptosis. DNA double strand breaks activate ATM, thereby initiating cell apoptosis. Granular cells are usually targeted due to their characteristics of mitosis and active metabolism [16]. Anthracyclines also intercalate into DNA, impairing DNA replication, RNA and protein synthesis. Anthracycline-based drugs induce fibrosis in human ovaries and have been shown to penetrate the follicular basement membrane and accumulate in oocyte DNA and mitochondria. The late stage of follicular development is also affected by anthracycline drugs, leading to a decrease in secondary and antral follicles. In addition, anthracycline drugs also reduce ovulation rates[14].

1.2.4 Taxanes

The key molecular mechanisms of taxanes include disruption of the mitotic spindle, mitotic slip, and inhibition of angiogenesis [19]. Taxanes can cause depletion of ovarian follicular pools, but they do not cause direct damage to ovarian blood vessels [20]. The mechanism of the impact of receiving paclitaxel chemotherapy on ovarian function in patients is still uncertain. The correlation obtained in animal models indicates that paclitaxel drugs significantly affect the number of follicles [21], and there is also data indicating

that paclitaxel can reduce antral follicles and increase atresia follicles, but does not affect the number of primordial follicles [22]. In addition, paclitaxel also inhibits the expression of follicle development related genes, growth differentiation factor 9 (GDF9), and bone morphogenetic protein 15 (BMP15) [23]. Taxane-based treatments impair ovarian granulosa cells and oocytes, resulting in follicle death or aneuploidy [24].

1.3 Real-World data

A study conducted in 8 institutions in China randomly assigned 521 women with a median age of 34 years to receive either adjuvant epirubicin and cyclophosphamide followed by weekly paclitaxel (EC-wP) or non-cyclophosphamide regimens followed by weekly paclitaxel (EP-wP). The research results indicated that 12 months after chemotherapy, a higher proportion of women in the non-cyclophosphamide group recovered ovarian function (63.1% and 48.3%), and achieved post-treatment pregnancy (9.0% and 2.7%). This study tried to exclude the influence of age, dosage, and number of chemotherapy cycles as much as possible, and verified the effect of cyclophosphamide on ovarian function.

A study showed that the frequency of chemotherapy related menopause in women receiving the CMF regimen (33.3%) was higher than that in women receiving the FAC (11.3%) or AC-D or AC-T (13.0%) regimens, but the difference was not statistically significant (P=0.284) (C: cyclophosphamide, M: methotrexate, F: fluorouracil, A: doxorubicin, D: docetaxel) [26]. Since the impact of chemotherapy on female ovarian function has been studied, anthracycline-based drugs and alkylating agents have been clearly shown to have a significant impact on ovarian function. However, this study reveals another aspect where the impact of chemotherapy on ovarian function can vary with different drug combinations.

In anthracycline-based chemotherapy regimens, the amenorrhea rate (38.9%) of patients who did not use paclitaxel (n=18) was significantly lower than that of patients who used paclitaxel (n=13) for 12 weeks per week (69.2%) and those who used docetaxel for 4 cycles every 3 weeks (66.7%) [9]. Adding taxanes to chemotherapy regimens based on anthracycline drugs increases the risk of amenorrhea. However, this study contradicts previous research, suggesting that taxane-based drugs have a more detrimental impact on ovarian function compared to anthracycline-based drugs.

A study included 100 breast cancer patients with an average age of 36 years. The incidence of chemotherapy-induced amenorrhea was 82%, and 66.7% of the patients resumed menstruation. An analysis of risk factors associated with chemotherapy-induced amenorrhea revealed a statistically significant difference based on the patient's age at diagnosis [27]. As women age, their ovarian function gradually declines, and the external manifestation is menopause. Therefore, most studies suggest that patient age also influences the extent of ovarian damage and recovery during chemotherapy.

There is also data indicating that the higher the dose intensive/dose intensified regimen and treatment time for patients, the higher the rate of chemotherapy induced ovarian failure [9,26,28]. While further understanding the mechanism of the influence of chemotherapy drugs on ovarian function in breast cancer, the real influence of actual drugs on human body cannot be ignored. Based on real-world data, the impact of these drugs on ovarian function should not only consider the drug itself, but also the differences in chemotherapy cycle, chemotherapy frequency, chemotherapy dose, as well as the impact of the patient's basic ovarian function and age on the results.

2 Drugs for preventing and treating ovarian damage caused by chemotherapy

Until now, the freezing and preservation of oocytes and embryos are still the standard options for preserving fertility in young patients who hope to retain fertility in future pregnancies. There are also studies mentioning the cryopreservation technology of ovarian tissue, which can be transplanted back to the patient after completion of treatment [29]. This method is more suitable for girls before puberty. In addition, with the increasing attention paid to the preservation of fertility after cancer treatment, some drugs related to ovarian protection have also emerged in recent years.

2.1 GnRHa

GnRHa has a protective effect on ovarian function, but its molecular mechanism is not yet clear. The relevant molecular mechanisms include simulating a low gonadotropin environment before puberty, reducing ovarian blood flow perfusion, mediating direct effects on the ovaries through GnRH receptors, potentially protecting ovarian reproductive stem cells, and anti-apoptotic effects on cumulus cells [30]. But there are also other reports revealing different molecular mechanisms. GnRHa induces autophagy by regulating the mTOR signal, thereby alleviating estrogenic receptor stress induced by cyclophosphamide and promoting the secretion of AMH [31]. Although the molecular mechanisms of GnRHa are not well understood, it is still a valuable drug for the prevention of chemotherapy-induced ovarian dysfunction in clinical practice. Some studies have shown that GnRHa combined with chemotherapy seems to prevent ovarian failure, reduce the risk of early menopause, and improve fertility prospects [6,32-33]. Although GnRHa may have a protective effect on the occurrence of ovarian premature failure after chemotherapy, the duration of its benefits is not yet clear. Some studies have reported that the benefits of GnRHa treatment seem to diminish two years after the end of chemotherapy [34]. Although the fertility protection potential of GnRHa used during chemotherapy is still controversial, it is also the standard strategy for preserving ovarian function in premenopausal early breast cancer patients.

2.2 Granulocyte colony stimulating factor (G-CSF)

G-CSF is currently considered a drug that may have a protective effect on ovarian function in animal experiments. The mechanism is that G-CSF promotes ovarian function recovery by increasing ovarian neovascularization, reducing granulosa cell apoptosis, and promoting follicle formation. In adult female rat experiments, G-CSF mobilization of peripheral blood mononuclear cells combined with platelet rich plasma can restore ovarian function in cyclophosphamide induced ovarian insufficiency rats [35]. Some studies have also found that G-CSF can restore ovarian function damage induced by cyclophosphamide in female rats, and the combination of G-CSF and bone marrow stromal cells has a higher therapeutic effect on chemotherapy induced ovarian recovery [36]. In a cisplatin induced rat model, G-CSF can alleviate cisplatin induced ovarian damage in rats [37]. But these preclinical research results need to be further validated in humans and compared with established GnRH analogues for therapeutic efficacy.

2.3 Tamoxifen

Tamoxifen is an estrogen antagonist used in hormone dependent breast cancer, and is currently being explored as a potential fertility preserver. In the latest research progress, further exploration has been conducted on its mechanism of protecting ovarian function. The protective effect of tamoxifen on rat ovaries is partially achieved by reducing cell apoptosis [38]. Besides, transcriptomic and proteomic screening indicate that DNA repair pathways, cell adhesion, and extracellular matrix remodeling play important roles in tamoxifen's ovarian protection. Previous experiments have also shown that tamoxifen protects primordial follicles from oxidative stress by upregulating insulin-like growth factor (IGF-1) [38]. However, this also lacks corresponding clinical trials and requires further validation.

Some anti-tumor drugs have also shown their ovarian protective effects, such as imatinib, a widely used tyrosine kinase inhibitor, which is currently one of the first-line options for treating chronic myeloid leukemia (CML). It can inhibit the C-ABL kinase mediated apoptosis pathway [39], and the accumulation of ABL in oocytes can lead to oocyte death, highlighting the possibility of imatinib playing an anti-apoptotic role in ovarian primordial follicles. But at the same time, studies have proposed the opposite view on the anti-apoptotic effect of imatinib, which may exert ovarian toxicity through the process of cell apoptosis [40]. In the latest research progress, AS101, as a PI3K/AKT signaling pathway modulator, has also raised doubts about the protective effect of imatinib on ovarian function [41]. AS101 is also another ovarian protective agent that can act as an ovarian protector by reducing the activation and subsequent failure of quiescent ovarian follicles [42]. In addition, sphingosine-1-phosphate (S1P) seems to exhibit inconsistent ovarian protective functions. Studies have shown that S1P plays an important role in ovarian physiology, participating in follicle development in the pre antral and sinus phases, and playing an important stimulating role in ovulation and luteal development. It may be a good cell protective agent against chemotherapy side effects [43]. But in contrast, Krüppel like factor 12 (KLF-12) regulates aging ovarian granulosa cell apoptosis by inhibiting the production of S1P [47]. Luteinizing hormone (LH), one of the gonadotropins, has also been proposed to protect the follicular pool of prepubescent mice from the effects of cisplatin in recent studies [45]. These drugs have shown some effectiveness in animal experiments, but there are also conflicting aspects that require further preclinical trials and validation in order to obtain more effective drugs and benefit humanity.

3 Ovarian function indicators

For women receiving chemotherapy for breast cancer, it is recommended to conduct basic ovarian reserve test to assess future fertility and track ovarian function after treatment. Baseline testing can help identify individuals at risk of declining ovarian reserve and provide a baseline for evaluating changes during treatment. The evaluation includes basal follicle estrogen (FSH) and estradiol (E2), AMH, and sinus follicle count (AFC) on transvaginal ultrasound examination. At present, FSH and E2 are still important indicators for evaluating ovarian function, but due to their greater influence on female menstruation, the measurement results may have some deviation. AMH is produced by granulosa cells of small follicles growing in the ovary. Serum AMH levels are closely correlated with the number of growing follicles and are increasingly recognized as a marker of ovarian reserve. Studies have shown that early analysis of AMH after chemotherapy can effectively identify women with irreversible ovarian function [46]. AFC and serum AMH concentration measured by transvaginal ultrasound can accurately reflect the antral follicle pool, providing more sensitive and specific results [47].

4 Summary

With the increasing incidence of breast cancer, the protection of fertility after treatment of breast cancer has become the focus of attention. In particular, the pregnancy rate after chemotherapy is significantly lower in women with breast cancer compared to their age-matched counterparts. Although its potential mechanisms have gradually been discovered, including direct resting follicle DNA damage, inducing mature and functional ovarian follicle apoptosis and damaging the ovarian vascular system, but the currently available fertility protection schemes and their associated costs are not encouraging. Cryopreservation of oocytes and embryos remains the standard choice for preserving fertility in young patients hoping for future conception, but it may not be readily available within the same facility and a significant timeframe. In these cases, the

use of GnRHa may be considered, but their protection against fertility remains partially controversial, although it is currently the standard strategy for preserving ovarian function in premenopausal patients. The remaining ovarian protectants, including G-CSF, tamoxifen, AS101, and S1P, are still in the preclinical trial stage and lack clinical trial data.

Excluding objective factors, doctors and patients often do not place enough emphasis on fertility during diagnosis. Considering the nature of cancer as a disease, patients often feel overwhelmed by this diagnosis and urgently need to start active treatment. Many patients and families believe that pursuing fertility preservation may delay their treatment. It is still a challenge to establish the awareness of fertility preservation of patients during the treatment of breast cancer and other cancers. The management of young female patients with breast cancer is multifaceted, which needs to be considered in many ways, and more targeted treatment interventions should be carried out for different problems.

Conflict of interest None

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· 研究进展 ·

乳腺癌化疗药物对卵巢功能影响研究进展

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摘要：在具有生育潜能的女性中，乳腺癌化学治疗导致的卵巢功能紊乱具有深远的影响。卵巢功能减退短期可表现为停经、月经紊乱、潮热盗汗、生育能力受损，远期可表现为心血管风险增加、骨密度降低、认知功能障碍等。化疗药物导致卵巢功能减退与药物种类、接受化疗的次数、化疗的剂量、患者的年龄有密切相关性。卵巢功能的保护药物众多，但在临床应用目前仍以促性腺激素释放激素激动剂（GnRHa）为主，其他卵巢保护药物普遍缺乏临床实验数据，其安全性以及对化疗疗效的影响仍待进一步的研究。

关键词：乳腺癌；卵巢储备功能；辅助化学治疗；环磷酰胺；促性腺激素释放激素激动剂；铂类；蒽环类；紫杉烷类；生育力保护；戈舍瑞林；他莫昔芬

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Research progress on the effect of chemotherapy drugs on ovarian function in breast cancer

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Abstract: In women with reproductive potential, ovarian dysfunction caused by chemotherapy for breast cancer has far-reaching effects. Ovarian insufficiency can manifest as amenorrhea, menstrual disorders, hot flashes and night sweats, impaired fertility in the short term, and increased cardiovascular risk, reduced bone density, cognitive impairment in the long term. The occurrence of ovarian insufficiency due to chemotherapy is closely related to the type of drug, the number of chemotherapy sessions, the dose of chemotherapy, and the age of the patient. There are many drugs for protecting ovarian function, but in clinical practice, gonadotropin-releasing hormone analogues (GnRHa) are still the mainstay. Other ovarian protection drugs generally lack clinical trial data, and their safety and impact on chemotherapy efficacy need further research.

Keywords: Breast cancer; Ovarian reserve function; Adjuvant chemotherapy; Cyclophosphamide; Gonadotropin-releasing hormone agonists; Platinum; Anthracycline; Taxane; Fertility preservation; Goserelin; Tamoxifen

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乳腺癌发病年龄在近几年趋于年轻化，将近 10% 的乳腺癌病例发生在 45 岁以下的妇女中[1]。在现有的文献中，有乳腺癌病史的妇女的妊娠率平均比一般人群低 40%～60%[2]。随着我国经济水平和生活质量的提高，女性婚育观念发生改变，晚婚晚育的女性占比逐渐升高，致使较多育龄期女性在诊断乳腺癌时还未生育。随着生存率的提高，年轻女性癌症患者的生育和生殖问题受到了越来越多的关注。

目前乳腺癌的治疗主要为三种系统模式：化疗、内分泌治疗和靶向治疗[3]。化疗药物在帮助乳腺癌患者提高生存率（OS）、延长无进展生存期（PFS）的同时，也对患者全身各组织器官产生影响。对于女性，在这些化疗副作用中，早发性卵巢功能不全可能会对其终生的整体健康造成负面影响，导致不孕和短—长周期。保留卵巢功能与许多绝经前妇女高度相关，无论其年龄和怀孕愿望如何。与以前的指南一致，将“年轻女性”定义为乳腺癌诊断时年龄小于 40 岁的女性，与老年女性乳腺癌相比，年轻女性乳腺癌的特点是侵袭性表型的肿

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瘤比例较高[4],化疗药物种类、接受化疗的次数、化疗的剂量相比于老年女性会有一定程度的升级,但年龄应与其他因素一起考虑,而不应是拒绝或推荐治疗的唯一决定因素。在年轻的绝经前患者中,应讨论生育问题,并在患者希望的情况下,在开始任何系统治疗之前,应讨论生育力保存技术[5]。在化疗期间使用促性腺激素释放激素激动剂(GnRHa)获得的卵巢抑制,目前被推荐作为保留绝经前乳腺癌患者卵巢功能的策略,但不能作为独立的生育力保存技术[6]。但目前现有的指南中,未曾提及卵巢保护剂是否可以完全或最大程度的保护卵巢功能。本综述旨在总结常见乳腺癌化疗药物对卵巢功能的影响,寄予将来通过化疗药物的选择,化疗药物的配伍,在不影响患者生存质量的情况下,选择更适合育龄期乳腺癌患者的化疗方案。

1　乳腺癌化疗药物对卵巢功能影响

1.1　*病理生理学*　关于化疗引起的性腺毒性的潜在病理生理学,已经提出了多种机制,包括卵巢组织缺血、卵泡凋亡、卵泡死亡、卵泡的破坏等。卵巢组织缺血可能是由于化疗药物导致血管收缩或抑制血管生成引起[7]。卵泡凋亡直接源于 DNA 交联/嵌入或通过 DNA 甲基化抑制蛋白质合成。卵泡死亡也可能来自于卵泡周期的破坏,因为微管组装的抑制可以使卵泡停滞在中期[8]。卵泡的破坏导致抗苗勒管激素(anti-Müllerian hormone, AMH)的丢失,原始卵泡池的抑制被削弱,原始卵泡被过度激活。细胞毒性化疗药物耗尽卵巢储存和损害卵巢功能以及生育能力。

1.2　*分子机制*　在哺乳动物中,卵巢储备在生命早期就已经建立,然后在整个生殖年中有规律地下降。化疗可对卵巢储备功能产生不利影响[5,9]。化疗引起的闭经可能是一过性的,治疗结束后月经可能恢复。但月经恢复不完全代表卵巢功能的恢复。卵母细胞和颗粒细胞易受化疗药物的影响[10]。每种药物对癌细胞可能有不同的作用机制,导致细胞周期的停止。原始卵泡的过度生长,通过直接和间接的细胞毒性作用,导致过早和不可逆的生长卵泡耗竭,这被称为“细胞毒性”。还有 PI3K/PTEN/Akt 通路的激活和卵泡“倦怠”效应[11],以及卵巢萎缩伴纤维化[12]等性腺毒性机制。同时最新研究表明化疗药物通过增加活性氧生成,过度诱导的脂质过氧化和线粒体功能障碍引发卵巢细胞铁死亡,导致卵巢细胞死亡[13]。乳腺癌化疗药物中已知的性腺毒性化疗药物,包括目前治疗方案常用的环磷酰胺、蒽环类、紫杉类以及铂类等。

1.2.1　环磷酰胺类烷化剂　环磷酰胺本身是一种前药,在肝脏中被细胞色素 P450 代谢形成 4-羟基环磷酰胺,进而转化为磷酰胺氮芥和丙烯醛。磷酰胺氮芥是主要的活性代谢物,诱导 DNA 交联,导致形成加合物,从而阻止 DNA 复制。磷酰胺氮芥还会影响线粒体,导致跨膜电位和细胞质细胞色素 C 积累减少[14]。烷化剂是导致卵巢氧化应激增加的主要原因,甚至可以攻击储备卵泡池,导致 DNA 断裂,无论细胞分裂如何。尽管存在剂量依赖性效应,但低剂量时也可能发生卵泡破坏[10]。随后积累的 DNA 链断裂激活了细胞内的促凋亡途径,导致受影响的卵巢卵泡凋亡[8]。环磷酰胺还可以通过消耗原始卵泡,损伤卵巢功能[15]。

1.2.2　铂类药物　由重金属组成,作为 DNA 交联剂,干扰 DNA 修复机制、阻止细胞分裂、引发 DNA 损伤并引发细胞凋亡[14]。通过形成链间/链内 DNA 加合物,干扰细胞转录和复制,造成 DNA 损伤。abl 和 TAp63-α 蛋白在卵母细胞中的积累导致其死亡[16]。铂类通常被认为具有中度的卵巢毒性。除了与 DNA 共价结合外,铂类还可以与细胞核和细胞质蛋白结合,这可能会对患者产生不良毒性作用[17],增加它的性腺毒性。

1.2.3　蒽环类药物　蒽环类药物是治愈性乳腺癌化疗的高效组成部分,主要是通过抑制拓朴异构酶-Ⅱ与 DNA 的作用,阻止其复制和转录[18]。在高水平 DNA 损伤的情况下,P53 蛋白上调诱导细胞凋亡。DNA 双链断裂导致 ATM 的激活,从而启动细胞凋亡。颗粒细胞通常由于其有丝分裂和代谢活跃的特性而被靶向[16]。蒽环类还嵌入到 DNA 中,损害 DNA 复制和 RNA 及蛋白质合成。蒽环类药物在人类卵巢中诱导纤维化,已被证明可以穿过卵泡基底膜,并在卵母细胞的 DNA 和线粒体中积累。卵泡发育的后期阶段也受到蒽环类药物的影响,导致次级和有腔卵泡减少。此外,蒽环类药物还降低了排卵率[14]。

1.2.4　紫杉烷类药物　紫杉烷类化合物的关键分子机制包括破坏有丝分裂纺锤体、有丝分裂滑移和抑制血管生成[19]。紫杉烷类会造成卵巢滤泡池的耗竭,但不会造成直接的卵巢血管损伤[20]。接受紫杉烷类化疗对患者的卵巢功能影响机制仍不确定。在动物模型中获得的相关数据表明紫杉烷类药物显著影响卵泡的数量[21],也有数据表明紫杉醇可减少窦卵泡并增加闭锁卵泡,但不影响原始卵泡的数量[22]。此外,紫杉醇还抑制卵泡发育相关基因、生长分化因子 9(GDF9)和骨形态发生蛋白 15(BMP15)的表达[23]。紫杉烷类药物治疗会损害卵巢颗粒细胞和卵母细胞,导致卵泡死亡或非整倍体[24]。

1.3　*真实世界数据*　一项在中国的 8 个机构中进行的研究,将 521 名中位年龄为 34 岁的女性随机分配到接受辅助表柔比星和环磷酰胺后每周紫杉醇(EC-wP)或无环磷酰胺方案的表柔比星和紫杉醇后每周紫杉醇(EP-wP)[25]。研究结果表明化疗结束后 12 个月,无环磷酰胺组有更大比例的女性恢复卵巢功能(63.1%和 48.3%),并有治疗后妊娠(9.6%和 2.7%)。该项研究尽可能排除年龄、剂量、化疗次数的影响,验证了环磷酰胺对卵巢功能的影响。

研究表明接受 CMF 方案的女性发生化疗相关性绝经的频率(33.3%)高于接受 FAC(11.3%)或 AC-D 或 AC-T(13.0%)方案的女性,但差异无统计学意义($P=0.284$)(C:环磷酰胺,M:甲氨蝶呤,F:氟尿嘧啶,A:多柔比星,D:多西他赛)[26]。自关注化疗对女性卵巢功能影响以来,蒽环类药物、烷化剂就被明确对卵巢功能有巨大影响。但这个研究显现出了另一方面,不同药物配伍的情况下,化疗对卵巢功能的影响也有所不同。

以蒽环类药物为基础的化疗方案中,未使用紫杉类($n=$

18)的患者闭经率(38.9%)显著低于每周使用紫杉醇(n=13)12 周的患者(69.2%)和每 3 周使用多西他赛 4 周期的患者(66.7%)[9]。在以蒽环类药物为基础的化疗方案中加入紫杉类药物增加了闭经的风险。但这项研究则与之前研究有所矛盾,紫杉烷类药物相比于蒽环类药物有着更差的卵巢功能影响。

一项研究纳入 100 名平均年龄为 36 岁的乳腺癌患者,化疗致闭经的发病率为 82%,66.7%的患者恢复了月经。分析与化疗致闭经相关的危险因素,发现诊断时的患者年龄与化疗致闭经差异有统计学意义[27]。女性随着年龄的增长,卵巢功能逐渐衰减,外在表现为绝经。所以研究表明,患者的年龄也会影响卵巢功能在化疗过程中的损伤及恢复程度。

另有数据表明,患者剂量密集/剂量强化方案、治疗时间越长,化疗引起卵巢功能衰竭率越高[9,26,28]。在进一步了解乳腺癌化疗药物对卵巢功能影响机制的同时,也不能忽略实际药物作用于人体的真实影响。结合真实世界的数据,这些药物对卵巢功能的影响,除了药物本身,还要考虑化疗周期、化疗次数、化疗剂量等差异的影响,以及患者本身的基础卵巢功能和年龄对结果的影响。

2　防治化疗药物引起卵巢损伤的药物

直到目前卵母细胞和胚胎冷冻保存仍是希望未来受孕的年轻患者保留生育能力的标准选择。还有研究提及卵巢组织冷冻保存技术,待患者完成治疗后再移植给患者,这种方法也更适用于青春期前的女孩[29]。随着社会对癌症治疗后生育力保存的关注,近年来也出现了部分卵巢保护的相关药物。

2.1　GnRHa　GnRHa 具有保护卵巢功能的作用,但其分子机制尚未明确。有文献总结了相关的分子机制包括:模拟青春期前低促性腺激素环境,减少卵巢血流灌注,通过 GnRHa 受体介导对卵巢的直接作用,可能对卵巢生殖干细胞有保护作用以及对卵丘细胞的抗凋亡作用等[30]。但也有另外的报道揭示了不同的分子机制。GnRHa 通过调节 mTOR 信号诱导自噬,从而缓解环磷酰胺诱导的雌激素受体应激,并促进 AMH 的分泌[31]。尽管 GnRHa 的分子机制不是很明朗,但其在临床治疗中仍是有价值的预防化疗性卵巢功能障碍的药物。部分研究表明 GnRHa 戈舍瑞林联合化疗似乎可以预防卵巢功能衰竭,降低早期绝经的风险,改善生育前景[6,32-33]。虽然 GnRHa 对化疗后卵巢早衰的发生可能有保护作用,但其获益的持续时间尚不清楚,有研究报道化疗结束后两年,GnRHa 治疗的获益似乎并没有持续存在[34]。尽管化疗期间使用 GnRHa 的生育力保护潜力仍存在争议,但这也是目前绝经前早期乳腺癌患者保留卵巢功能的标准策略。

2.2　粒细胞集落刺激因子(G-CSF)　G-CSF 目前在动物实验中被认为有可能对卵巢功能起到保护作用。其机制是 G-CSF 通过增加卵巢新生血管,减少颗粒细胞凋亡,促进卵泡生成,从而促进卵巢功能的恢复。在成年雌性大鼠实验中,G-CSF 动员外周血单个核细胞联合富血小板血浆可以恢复环磷酰胺诱导的卵巢功能不全大鼠的卵巢功能[35]。也有研究发现 G-CSF 可恢复环磷酰胺诱导的雌性大鼠卵巢功能损伤,G-CSF 联合骨髓基质细胞治疗对化疗损伤卵巢恢复中的疗效更高[36]。在顺铂诱导的大鼠模型中 G-CSF 可减轻顺铂对大鼠卵巢的损伤[37]。但这些研究结果需要在人类中进一步进行验证,并与已建立的 GnRHa 治疗方案进行疗效比较。

2.3　他莫昔芬　他莫昔芬是一种应用于激素依赖性乳腺癌的雌激素拮抗剂,目前也被探索作为一种潜在的生育力保存剂。在最新的研究中也对其保护卵巢功能的机制有进一步的探究。他莫昔芬对大鼠卵巢的保护作用部分是通过减少细胞凋亡实现的[38],此外,转录组学和蛋白组学筛选表明 DNA 修复途径以及细胞黏附和细胞外基质重塑在他莫昔芬对卵巢保护作用中起到重要作用。既往也有实验表明,他莫昔芬通过上调胰岛素样生长因子(IGF-1),从而保护原始卵泡免受氧化应激的影响[38]。然而这同样缺乏相应的临床实验。

部分抗肿瘤药物也呈现了其保护卵巢功效,如一种广泛使用的酪氨酸激酶抑制剂——伊马替尼,是目前治疗慢性粒细胞白血病(CML)的一线选择之一,可以抑制 c-abl 激酶介导的凋亡途径[39],而 abl 在卵母细胞中的积累可导致卵母细胞死亡,突显出伊马替尼在卵巢原始卵泡中发挥抗凋亡作用存在一定可能性。但同时有研究对伊马替尼的抗凋亡作用提出了相反的观点,伊马替尼可能通过细胞凋亡过程发挥卵巢毒性[40]。在最新的研究进展中,AS101 作为 PI3K/AKT 信号通路调节剂也对伊马替尼保护卵巢功效提出了质疑[41]。AS101 也是一种卵巢保护剂,可以通过减少卵巢静止卵泡的激活和随后的衰竭,从而起到卵巢保护的作用[42]。此外鞘氨醇-1-磷酸盐(S1P)似乎也体现了不一致的卵巢保护功能,研究表明 S1P 在卵巢生理中起着重要的作用,在窦前和窦状期参与卵泡发育,在排卵和黄体发育中起着重要的刺激作用,可能是对化疗副作用的良好细胞保护剂[43]。但与其相对立的是 Krüppel-like factor 12(KLF-12)通过抑制 S1P 的产生来调节衰老的卵巢颗粒细胞凋亡[44]。促性腺激素之一的促黄体生成素(LH)在近年的研究中也被提出可以保护青春期前小鼠的卵泡池免受顺铂的影响[45]。这些药物在动物实验中都有部分成效,但也不乏相互矛盾的部分,需要进一步的临床前试验、验证,以期获得更多的有效药物。

3　卵巢功能指标

因乳腺癌接受化疗的女性,建议进行基础卵巢储备检测,以评估未来的生育能力和跟踪治疗后的卵巢功能。基线检测可能有助于识别卵巢储备功能下降的风险人群,并为评估治疗过程中的变化提供基准。评估包括基础卵泡雌激素(FSH)和雌二醇(E2)、AMH 和经阴道超声检查的窦卵泡计数(AFC)等。目前 FSH 和 E2 仍是评估卵巢功能的重要指标,但因其受女性月经影响较多,测量结果可能会出现些许偏差。AMH 是由卵巢生长中的小卵泡的颗粒细胞产生的。血清 AMH 水平与生长中的卵泡数量密切相关,AMH 作为卵巢储备的标志物越来越受到关注。有研究表明,化疗后对 AMH 的早期分析可以很好地识别出卵巢功能无法恢复的女性[46]。经阴道超

声测量的 AFC 和血清 AMH 浓度可准确反映窦卵泡池,提供更敏感和特异性的结果[47]。

4　小　结

随着乳腺癌发病率的增加,乳腺癌治疗后的生育力保护成为人们关注的焦点。特别是在女性乳腺癌患者中,与同龄女性相比,化疗后妊娠率明显降低。尽管其潜在的机制逐步被发现,包括直接静息卵泡 DNA 损伤;诱导成熟的、有功能的卵巢卵泡凋亡以及损害卵巢血管系统等,但目前可供选择的生育率保护方案及其相关成本也并不尽如人意。卵母细胞和胚胎冷冻保存是希望未来受孕的年轻患者保留生育能力的标准选择,但卵子或胚胎冷冻保存可能无法在同一设施和大量时间内获得。在这些情况下,可考虑使用 GnRHa,但其对生育力的保护仍存在部分争议,尽管它是目前绝经前患者保留卵巢功能的标准策略。其余卵巢保护剂,包括 G-CSF、他莫昔芬、AS101 及 S1P 等,目前仍处于临床前实验阶段,缺乏临床实验数据。

除去客观因素,在诊断时,医生和患者通常都不够重视生育能力。考虑到癌症作为一种疾病的性质,患者通常对这种诊断感到不知所措,迫切需要开始积极治疗,许多患者和家庭认为追求生育力的保存可能会推迟她们的治疗。建立乳腺癌乃至其他癌症治疗过程中患者保存生育力意识仍然是一个挑战。年轻女性乳腺癌患者的管理是多方面的,需要多方考虑,针对不同问题进行更有针对性的治疗干预。

利益冲突　无

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