Correlation of Premature ovarian insufficiency with chemotherapy treatment

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ABSTRACT

The reserve of ovarian follicles is very vulnerable from the impact of chemotherapy and radiation therapy, therefore anti-cancer treatment is frequently a reason from infertility and early inadequacy of the ovaries. The creation of efficient strategies to safeguard when undergoing chemotherapy, ovarian function would be impaired a huge usefulness, even though cryopreservation of oocytes, embryos, and ovarian cortex can assist many females with cancer-induced infertility in becoming pregnant. This study critically examines the various detrimental effects of the most widely used chemotherapy drugs in relation to the ovary, namely the follicles of the ovary, as well as the molecular mechanisms that underlie those adverse effects. The processes by which follicle loss brought on by chemotherapy drugs might be prevented by fertility-protective drugs are then reviewed. According to recent research, chemotherapy medicines can have an impact on the ovary's many cellular elements, rapidly depleting the ovarian follicular reserve. By triggering the Primordial follicles die and/or quickly activate, as well as atresia of developing follicles, the top three important frequently Premature ovarian insufficiency is a side effect of the medications doxorubicin, cyclophosphamide, and cisplatin. Additionally, they exacerbate inflammation and injury to the stromal compartment and blood vessels.

Keywords: ovarian follicles

Introduction

Anticancer therapy and early detection advances have resulted in a rise in the proportion of cancer survivors who are younger [1]. Chemotherapy, in example, increases surviving in patients with cancer, although it can reduce life satisfaction by causing long-term premature ovarian failure is one of the negative effects (POI) [2], and irreversible infertility. POI is characterized as loss of ovarian function prior to the age of 40 [3].

POI is defined by at least four months of oligo/amenorrhea and two high follicle-stimulating hormone (FSH) values (> 25 IU/L) higher than four weeks apart [4]. severely reduced hypergonadotropism, ovarian reserve, unusually low estradiol levels, and inadequate ovarian responsiveness to circulating follicular stimulating hormone The onset rate of chemotherapy-induced amenorrhea (CIA) differs depending on the kind and the drug's dosage, the age of the patient, and the condition, and it ranges from 40 to 68 percent [5,6]. It is distinguished by a reduction in ovarian follicles and a reduction in hormone release. Despite the fact that frequency of POI has already been

reported to be between 0.9 and 1.2 % [7], a nationwide record research done in Sweden found that the overall prevalence of POI is around 1.9 % [8]. According to a new meta-analysis published by Golezar et al., 3.7 % of women globally are afflicted [9]. Long-term consequences for POI patients include osteoporosis, fractures, cardiovascular disease, and depression [10]. Moreover, this condition has a high potential for ruining parental expectations and goals.

Patients' fertility may be irreversibly harmed if POI is not diagnosed promptly. Other sensitive measures used to estimate ovarian reserves include anti-Mullerian hormone (AMH) and antral follicle count (AFC).

POI is a multifactorial condition as a result of hereditary factors, autoimmune disorders, mitochondrial abnormalities, iatrogenic causes (such as chemotherapy, radiation, and surgical operations), and ecological variables [11]. Furthermore, a considerable number of idiopathic POI patients, with no known cause [12]

Methods

A thorough search for relevant papers was conducted in order to conduct a comprehensive research into ovarian damage caused by chemotherapy and innovative ways from its prevention. The search, as well as selection and rejection criteria were developed by all authors. As an examination of publicly available data.

Ovarian insufficiency with chemotherapy treatment.

Cancer and its treatment are having an increasing impact on female reproductive function. females are 38 % fewer prone to become pregnant following Cancer detection and therapy, compared to the general population, with every testing groupings as a result of cancer related implies a lower likelihood of future pregnancies [13]. Given the current circumstances, there is an urgent need to create techniques to safeguard patients against the harmful consequences of therapy. As a result, this study evaluates the efficacy of various therapies to safeguard the ovary from the effects of chemotherapy.

While radiation and surgery will have a negative impact about woman reproductive functioning. The paper emphasizes the detrimental effects of chemotherapy as well as potential techniques to reducing their impact. The negative effects of chemotherapy on ovarian function have long been recognized (Fig. 1A), and there is a growing amount of evidence demonstrating the impact of various regimens on short-term ovarian function indicators, Longer-term fertility and the risk of early menopausal [14,15]. The impact of estrogen insufficiency caused by ovarian functionality loss on life quality, bone function, cardiovascular and neurological health are also important features from the long-term repercussions of chemotherapeutic ovarian harm [16,17].

The harmful effects from chemotherapeutic medicines on the ovary and possible countermeasures. (A) Chemotherapy medications can cause prenatal oogonia loss, Follicular atresia, stromal tissue injury, vascular damage, or inflammation can result from disappearance of primordial follicles directly, fast stimulation primitive follicles, or inflammatory. (B) Protectants studied thus far had been proven to guard against all ovarian cancers injury passage except those involving stromal tissue. Other safeguards are intended to minimize medication transport to the ovary. TRNS: transitional follicle; PMF: primordial follicle.

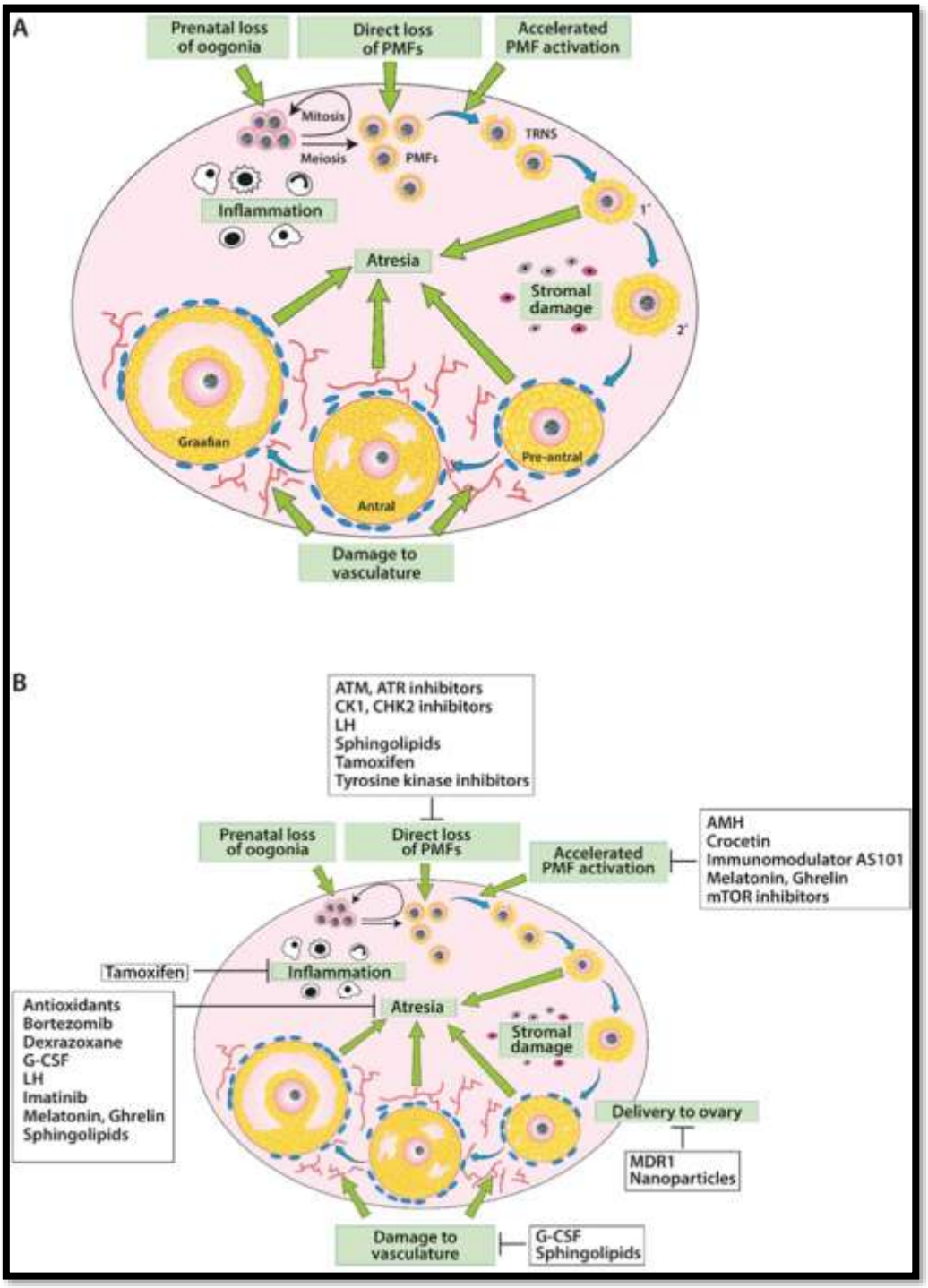

Figure 1: Ovarian function affected by chemotherapy and its prevention[15]

Ovarian damage from chemotherapy and its possibility

Chemotherapy ovarian damage and its possible protection Chemotherapy treatment's consequences about future fertility are significant for together pediatric malignancies including those affecting females up to menopause. Leukemia is the most frequent juvenile cancer (about 26% of all recorded cases), Tumors of the central nervous system and lymphomas come next. Carcinomas (about 30% of cases), lymphomas , melanoma and central nervous system tumors are the most prevalent in young women, whereas breast cancer (nearly 40% of cases) melanoma, in older premenopausal women, cervical cancer is the least prevalent, whereas central nervous system tumors are the largely prevalent [18].

The effects of chemotherapeutic medications on female fertility were first observed in the 1970s, and were first linked to CPM treatment [19-21], Amenorrhea, ovarian suppression, and follicular destruction have all been reported. From the beginning of the discovery of chemotherapy drugs, patients were treated using treatment combinations rather than single drugs. Given this, determining which specific medicine is to blame for the negative impacts on fertility has become increasingly challenging, very little known about certain drugs' ovarian toxicity treatments. Despite this, there is much clinical evidence showing alkylating and alkylating-like drugs cause severe ovarian damage [22-23], When DOX is used to treat a variety from malignancies, it is one of the absence of alkylation medicines the most closely connected with relation to female reproduction disorders [24,25]. As a result, many of the compounds being researched as possible protectants have been specially studied to mitigate harm caused by CPM, CIS, or DOX. As a result, each from these three medications' action mechanism and possible defense against harm are reviewed in depth below. It should be noted that some medications, especially the alkylating agent busulphan [26], cause mild to severe ovarian toxicity. In principle, some potential preservatives, such like AMH, must be effective against a wide range of pathogens. spectrum from chemotherapeutic medications.

Conclusion

Several possible approaches for shielding the ovary from chemotherapeutic drug harm have emerged throughout the last decade (Fig. 1). These safeguards are required not just to sustain but also to assist women in maintaining endocrine function while avoiding consequences of POI for health

Reference

1. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69(5):363–85. https://doi.org/10.3322/caac.21565.
2. Yu, L. (2022). Risk Prediction of Primary Ovarian Insufficiency in Childhood Cancer Survivors Using Polygenic Risk Scores and Clinical Risk Score.
3. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;376(9744):911–21. https://doi.org/10.1016/S0140-6736(10)60355-8.
4. Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926–37.
5. Apperley J, Reddy N. Mechanism and management of treatment-related gonadal failure in recipients of high dose chemoradiotherapy. Blood Rev. 1995;9(2):93–116. https://doi.org/10.1016/S0268-960X(95)90030-6.
6. Meirow D. Reproduction post-chemotherapy in young cancer patients. Mol Cell Endocrinol. 2000;169(1-2):123–31. https://doi.org/10.1016/S0303-7207(00)00365-8.
7. Pastorello, M., Gastal, M. O., Godoi, D. B., & Gastal, E. L. (2022). Emergence and selection of the dominant follicle and gonadotropin dynamics in postpartum lactating versus non-postpartum cycling mares. Reproductive Biology, 22(2), 100618.
8. Lagergren K, Hammar M, Nedstrand E, Bladh M, Sydsjö G. The prevalence of primary ovarian insufficiency in Sweden; A national register study. BMC Womens Health. 2018;18:175.
9. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. Climacteric. 2019;22:403–11.
10. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;376:911–21.
11. Rudnicka E, Kruszewska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, et al. Premature ovarian insufficiency - aetiopathology, epidemiology, and

diagnostic evaluation. Prz Menopauzalny. 2018;17:105–8.
12. Volozonoka, L., Miskova, A., Kornejeva, L., Kempa, I., Bargatina, V., & Gailite, L. (2022). A systematic review and standardized clinical validity assessment of genes involved in female reproductive failure. *Reproduction*, *163*(6), 351-363.
13. Anderson, R. A., Brewster, D. H., Wood, R., Nowell, S., Fischbacher, C., Kelsey, T. W., & Wallace, W. H. B. (2018). The impact of cancer on subsequent chance of pregnancy: a population-based analysis. *Human Reproduction*, *33*(7), 1281-1290.
14. Jayasinghe, Y. L., Wallace, W. H. B., & Anderson, R. A. (2018). Ovarian function, fertility and reproductive lifespan in cancer patients. *Expert review of endocrinology & metabolism*, *13*(3), 125-136.
15. Van Dorp, W., Haupt, R., Anderson, R. A., Mulder, R. L., Van den Heuvel-Eibrink, M. M., Van Dulmen-den Broeder, E., ... & Wallace, W. H. (2018). Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. Journal of Clinical Oncology, 36(21), 2169.
16. European Society of Human Reproduction and Embryology. Management of women with premature ovarian insufficiency, 2015
17. Lobo, R. A. (2017). Hormone-replacement therapy: current thinking. Nature Reviews Endocrinology, 13(4), 220-231.
18. Cronin, K. A., Lake, A. J., Scott, S., Sherman, R. L., Noone, A. M., Howlader, N., ... & Jemal, A. (2018). Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. *Cancer*, *124*(13), 2785-2800.
19. Miller III, J. J., Williams, G. F., & Leissring, J. C. (1971). Multiple late complications of therapy with cyclophosphamide, including ovarian destruction. *The American Journal of Medicine*, *50*(4), 530-535.
20. Fries, J. F., Sharp, G. C., Mcdevitt, H. O., & Holman, H. R. (1973). Cyclophosphamide therapy in systemic lupus erythematosus and polymyositis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *16*(2), 154-162.
21. Koyama, H., Wada, T., Nishizawa, Y., Iwanaga, T., Aoki, Y., Terasawa, T., ... & Wada, A. (1977). Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. *Cancer*, *39*(4), 1403-1409.
22. Chow, E. J., Stratton, K. L., Leisenring, W. M., Oeffinger, K. C., Sklar, C. A., Donaldson, S. S., ... & Green, D. M. (2016). Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. *The Lancet Oncology*, *17*(5), 567-576.
23. Van Dorp, W., Haupt, R., Anderson, R. A., Mulder, R. L., Van den Heuvel-Eibrink, M. M., Van Dulmen-den Broeder, E., ... & Wallace, W. H. (2018). Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. *Journal of Clinical Oncology*, *36*(21), 2169.
24. Bedoschi, G., Navarro, P. A., & Oktay, K. (2016). Chemotherapy-induced damage to ovary: mechanisms and clinical impact. *Future oncology*, *12*(19), 2333-2344.
25. Bedoschi, G. M., Navarro, P. A., & Oktay, K. H. (2018). Novel insights into the pathophysiology of chemotherapy-induced damage to the ovary. *Panminerva Medica*, *61*(1), 68-75.
26. Chow, E. J., Stratton, K. L., Leisenring, W. M., Oeffinger, K. C., Sklar, C. A., Donaldson, S. S., ... & Green, D. M. (2016). Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. The Lancet Oncology, 17(5), 567-576.