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Perspective

Fertility preservation for female patients with childhood and adolescent cancer

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With the significant cancer treatment in the past decades, > 85% of children with cancer now survives into adulthood, and fertility preservation has become an important quality-of-life technology for them.[1] Cancer treatment may include surgery, chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation (HSCT).[2] Except for non-pelvic surgery, these treatments may affect ovarian function and consequently cause varying degrees of gonadal toxicity.[3] Patients cured by anti-cancer treatment have a very high risk of premature ovarian insufficiency (POI).[4] At present, it is generally believed that not only the survival quantity of tumor patients should be improved, but also the quality of survival improved in ovary rescues should be equally important,[5]therefore, fertility preservation has become a key technology to achieve this goal.[6] However, previous evidence on cancer fertility counseling in the literature is insufficient In line with this evolution of cancer management, the vision of fertility preservation for young patients with cancer is additionally changing.The patients would be more concerned about the long-term quality of survival and fertility. Although providing fertility preservation before treatment initiation is important, addressing fertility across the cancer continuum is crucial.[7,8] The Pan-CareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group had provided recommendations for fertility preservation for childhood, adolescent, and young adult female cancer patients.[9] They suggested that fertility preservation methods that including oocyte, embryo cryopreservation, and ovarian tissue cryopreservation should be selected during all stages of anticancer treatments, according to the risk of infertility.[9] It is generally believed that oocyte cryopreservation may be more suitable for adolescent and ovary cryopreservation is the only choice for propubertal childhood.[6,10] These techniques are feasible, and multiple live births have been reported after their uses.[11] Meanwhile, for childhood and adolescent cancer patients, which methods of fertility preservation could be adopted and when they could receive fertility preservation counseling at different stages of anti-cancer treatment should be discussed more deeply and systematically.

1. Oocyte cryopreservation

Filippi et al. showed that POI is common among post-cancer patients of childhood and adolescent, oocyte cryopreservation is feasible.[12] As compared with slow freezing, vitrification of the oocyte significantly

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improves survival rate after thawing and results in higher pregnancy rates as well.[13] The birth rate is now 5%–6% per thawed oocyte.[14] However, oocyte cryopreservation could fulfill the reproductive requirements, rather than restore the ovarian activity. Moreover, we need to pay attention to the following issues[15]: First, in order to allow time for controlled ovarian stimulation (COS), chemotherapy needs to be delayed by at least 10 days, even if random-start protocols are used. Assuming that adolescents have a high number of follicles in the ovaries, one risk for these young females to develop ovarian hyperstimulation syndrome (OHSS) should be considered,[16] further delaying the start of chemotherapy or HSCT. Second, the patient must be postpubertal, as stimulation in the prepubertal period is effectiveness due to the absence of response to gonadotropins. Third, specific COS protocols are required depending on the steroid sensitivity of the specific cancer. Fourth, the information on oocyte quality in women with cancer is limited. After cancer treatment, patients should be advised to carry out consultation and evaluation of fertility preservation actively. Oocyte cryopreservation should be chosen according to the damage degree of ovarian function.

2. Ovary cryopreservation

International Guideline Harmonization Group pointed out that all children with cancer and their families have the right to be informed of the risk of gonadal damage and recommends that children and young patients who will receive a cumulative dose of 6000–8000 mg/m^2 or greater alkylating agent, ovarian radiotherapy, and HSCT undergo fertility preservation of ovarian tissue cryopreservation (OTC).[9] In 2019, American Society for Reproductive Medicine (ASRM) claimed that the OTC technique is no longer an experimental technique, thus it has become standard clinical fertility preservation technology.[17] If there is no natural menstrual cycle after cancer treatment, ovarian tissue transplantation can rebuild the ovarian function and fertility of patients. Ruan et al. studied the effectiveness and feasibility of fertility preservation in 49 children (≤14 years old) who faced gonadotoxic treatment, and proposed that OTC was the only method to preserve the fertility of prepubertal girls, and it is safe and effective. Chemotherapy before OTC is not a contraindication of OTC. However, at present no ovarian tissue re-transplantation of these patients has been completed, which induced the limited treatment experience.[10]

The acquisition and re-transplantation of ovarian tissue should be completed by surgery followed ovary cryopreservation. ASRM stressed the importance of surgical techniques in retrieving ovarian tissue and the importance of tissue preparation for cryopreservation, which is the core of the quality of cryopreservation and ultimately crucial to the success of the future application of ovarian tissue to restore fertility.[10] At present, laparoscopic unilateral oophorectomy is the first choice for surgery, which can maximize keeping of cortical tissues. Ruan showed that the median follicular count per 2-mm biopsy was 705. Chemotherapy before OTC reduced the level of AMH, but that had no significant impact on the number of follicles per 2mm biopsy.[10] Laparoscopic ovarian tissue retrieval has been proven safe for children and adults, with low intraoperative and postoperative risks, such as bleeding, infection, injury, etc. Ovarian tissue freezing methods include slow-programming and vitrification cryopreservation, so far slow-programming cryopreservation for ovarian tissue is internationally recognized as the gold standard procedure for OTC.[10]

Generally speaking, for all systemic malignant diseases, the risk of re-transplantation of malignant cells must be considered. Overcoming the risk of re-transplantation of malignant cells after childhood cancer must be -communicated with patients.[16] The risk of metastases should be weighed up according to cancer type. It is considered to be high (>11%) in case of leukemia, neuroblastoma and Burkitt lymphoma, and moderate (0.2%–11%) in case of advanced breast cancer, colon cancer, cervical adenocarcinoma, non-Hodgkin's lymphoma and Ewing sarcoma. The risk is deemed to be very low (<0.2%) in all other pathologies. In the case of any cancer, it is nevertheless recommended that ovary tissue fragment can be thawed for histological analysis, immunohistochemistry and polymerase chain reaction (when specific markers are available) before contemplating transplantation.[15] There are also limited reports on ovarian tissue re-transplantation in childhood and adolescent cancer patients. Therefore, more research is needed to explore the choice of re-transplantation time and the reconstruction of ovarian function and fertility after re-transplantation.

Ovarian tissue cryopreservation and transplantation are applicable to a wide range of patients, which is the only choice for fertility preservation for pre-pubertal patients and patients who need emergency radiotherapy and chemotherapy. However, the risk of ovarian metastasis of malignant tumors must be evaluated. Moreover, the psychological burden of childhood and adolescent cancer patients, as well as whether the time and cost required for treatment can be accepted by the patients and their families, should be considered carefully.

Dolmans et al. demonstrated that ovarian tissue cryopreservation does not impair oocyte number or quality followed immediately by COS and oocyte retrieval (with a view to vitrifying mature oocytes).[18] The combined technique increases the efficacy of the procedure, thereby giving young cancer patients greater chances of success.

3. Conclusion

For childhood and adolescent cancer patients, it is feasible balance anti-cancer treatment and fertility preservation. Moreover, fertility preservation must be carried out as early as possible before POI, and the consideration and selection should be made according to the indication and contraindication of different fertility preservation methods, such as the patient's age, type and stage of cancer and ovarian function,etc. Eliminating technical restrictions, the ethical, psychological issues and economic cost-effectiveness should also be considered during the treatment process. Therefore, more large-scale studies will be needed to provide clinical recommendations.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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