Radiotherapy-Induced Ovarian Damage

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Contributor: Seongmin Kim

Fertility preservation is an emerging discipline, which is of substantial clinical value in the care of young patients with cancer. Chemotherapy and radiation may induce ovarian damage in prepubertal girls and young women. Although many studies have explored the mechanisms implicated in ovarian toxicity during cancer treatment, its molecular pathophysiology is not fully understood.

chemotherapy radiotherapy gonadotoxicity fertility preservation embryo cryopreservation oocyte cryopreservation ovarian tissue cryopreservation oocyte in vitro maturation ovarian suppression oncofertility

1. Introduction

It is estimated that more than 9.2 million women were newly diagnosed with cancer worldwide in 2020 [1]. Furthermore, there were 89,500 new cancer cases and 9270 cancer deaths in adolescents and young adults (AYAs) aged 15–39 years in the United States [2]. The survival of cancer patients has significantly improved due to recent advances in cancer treatment [3][4]. However, oncologic therapies can affect ovarian function in young women [5][6][7][8]. The exhaustion of ovarian follicle reservoirs may lead to not only loss of fertility but also premature ovarian failure, which could result in poor quality of life in young female cancer survivors [9][10][11]. Recently, fertility preservation (FP) has become an emerging discipline with significant clinical value in the care of AYA cancer patients [12][13][14], and many organizations have provided recommendations for FP during cancer treatment [15][16][17][18][19].

Chemotherapy has toxic effects on the ovaries and causes the loss of the primordial follicle (PF) reserve [20]. Endocrine therapy can increase the risk of infertility in patients with hormone receptor-positive malignancies [21]. In the case of abdominal or pelvic cancers, treatments including radiotherapy or surgery may alter future fertility because of direct gonadal damage [22][23]. Many studies have explored the mechanisms implicated in ovarian toxicity during cancer treatment; however, the underlying molecular pathophysiology is not fully understood [24][25][26][27][28].

This article will review the mechanisms of cancer therapy-induced ovarian dysfunction and explore the future perspectives for preventing infertility in AYAs with cancer.

2. Cancer Treatment-Induced Ovarian Damage

Ionizing radiation to the abdominopelvic region has deleterious effects on gonadal function at all ages [29]. For example, cervical and rectal cancers usually require pelvic irradiation, and craniospinal radiotherapy is performed in cases of central nervous system malignancy. In some patients with Hodgkin's disease, pelvic lymph nodes require irradiation, and total body irradiation may be necessary prior to bone marrow transplantation.

The resulting damage depends on the dose and field of irradiation and the age of the patient. Women who received radiation treatment outside the pelvis had a low risk of ovarian dysfunction [30]. In the prepubertal period, the ovaries are relatively resistant to gonadotoxicity [31].

Dividing GCs appear to be the main target of radiation-related gonadotoxicity. Prominent cell death has been observed within a few hours of irradiation [32]. Oocytes are highly radiosensitive because the estimated dose at which half of the follicles are lost in humans (LD50) is <2 Gy [33]. A single oocyte is highly radiosensitive to a D 0 of 0.12 Gy (reciprocal of the slope of the exponential region of a survival curve). This sensitivity is affected by age; women younger than 40 years of age are less sensitive, requiring 20 Gy to experience permanent damage, whereas older women require only 6 Gy [34]. The radiosensitivity of oocytes differs according to their growth phase. A quiescent PF is usually more radio-resistant than a large maturing follicle [33]. Radiotherapy-induced ovarian damage also occurs in the stroma with vascular damage, resulting in tissue atrophy and fibrosis [32]. In general, a combination of multiple factors determines the extent of radiosensitivity, including age, the use of combination therapy, and radiation dose [35].

The biological effect of radiation treatment is also affected by linear energy transfer (LET) in tumors [36]. LET radiation induces anticancer effects by depositing physical energy or radiation into malignant cells, which results in stable free radicals and induces cellular damage because of the direct ionization of the cellular macromolecules, such as DNA, RNA, lipids, and proteins [37]. High LET radiation results in gonadal DNA damage that causes multiple lesions within the helical turns of the DNA, which is referred to as "direct" damage (**Figure 1**).

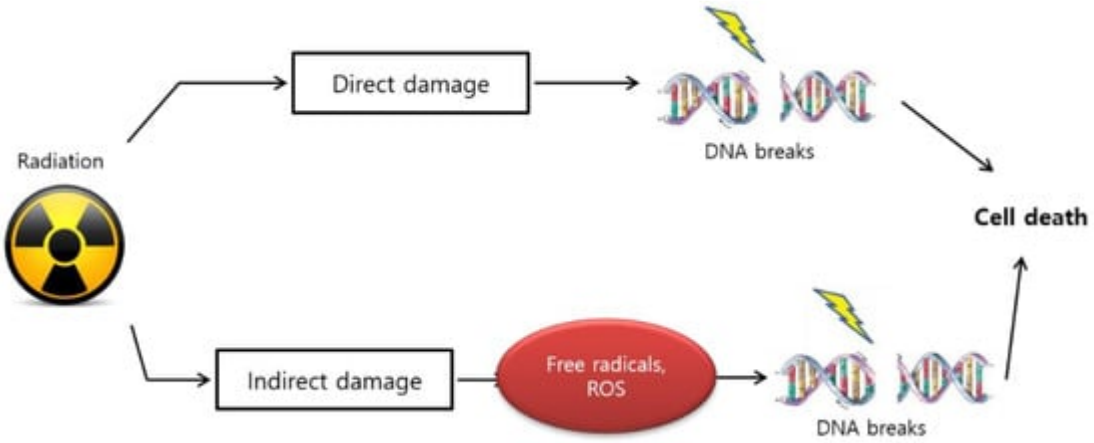

Figure 1. Biological effect of radiation via linear energy transfer (LET) in tumors. High LET radiation results in "direct" gonadal DNA damage that incorporates multiple lesions within the helical turns of the DNA molecule. Conversely, the increase in reactive oxygen species (ROS) induces rapid primordial follicle loss via "indirect" damage.

3. Detection of Ovarian Damage

However, the level of AMH does not always correlate with the quality of oocytes because it only reflects the quantity of oocytes [38]. Additionally, AMH concentration could be altered by the handling of the blood sample or the assay method used to measure AMH levels [39].

After chemotherapy, FSH levels usually increase due to follicular depletion. However, basal FSH is not always a valuable marker of ovarian reserve in patients who have undergone cancer treatment. For example, if women have regular menstrual cycles, FSH levels may show normal values, even though the ovarian reserve decreases after treatment [40][41]. In such instances, that is, when the FSH levels are within the normal range, estradiol concentration in the early follicular phase may provide additional information [42].

Inhibin-B is secreted by the GCs of antral follicles and it regulates FSH levels via a negative feedback reaction. Inhibin-B is usually exhibited at low levels in women with a decreased ovarian reserve [43]. However, it is not a reliable marker of the ovarian reserve because its levels vary widely during menstrual cycles [44].

During the early follicular phase, transvaginal ultrasound can be used to count antral follicles measuring 2–10 mm in both ovaries [45]. A low AFC may be related to a diminished response to ovarian stimulation. Furthermore, a few studies have demonstrated that a low AFC could be a marker for the risk of developing amenorrhea after cancer treatment [46][47]. However, the estimation of ovarian volume using ultrasound provides limited clinical utility as an ovarian reserve marker.

4. Prevention and Management of Ovarian Damage

As oocyte freezing involves the removal of cumulus cells before cryopreservation, it can induce changes in the zona pellucida, which may affect the fertilization rates of conventional insemination. Therefore, ASRM recommends intracytoplasmic sperm injection for frozen oocytes as the preferred procedure [48][49].

The combination of oocyte cryopreservation and ovarian tissue cryopreservation can enhance the results of the FP procedure [50]. However, the cryopreservation of ovarian tissue concomitant with oocyte retrieval is ineffective; thus, it is not recommended after ovarian stimulation with human menopausal gonadotropin or recombinant FSH followed by human chorionic gonadotropin [51][52].

Ovarian tissue cryopreservation is generally the only option for FP in children or AYAs with cancer who need immediate treatment and do not have enough time for ovarian stimulation and other procedures. Using this technique, a large number of oocytes, including PFs, can be preserved, and hormonal function of the ovary can be protected to improve the quality of life of the young patients [53].

Oocyte cryopreservation is not suitable for patients with ovarian or hematologic malignancies because of the possible contamination of the ovarian tissue with malignant cells, as shown in several studies [54][55]. Nonetheless,

ovarian tissue cryopreservation may be considered after an initial dose of chemotherapy to reduce the risk of malignant cell contamination, despite possible partial ovarian damage [56].

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