

EFFECTS OF BRACHYTHERAPY ON CYTOGENETIC PARAMETERS AND OXIDATIVE STATUS IN PERIPHERAL BLOOD LYMPHOCYTES OF GYNECOLOGIC CANCER PATIENTS

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Background: The state-of-the-art brachytherapy technologies with high-dose sources of ⁶⁰Co and ¹⁹²Ir within contemporary treatment protocols for cancer patients allow achieving maximum dose distribution in the clinical target and with minimum radiation exposure of surrounding organs and tissues. For minimization and overcoming the early and late radiation complications, development of respective radiobiological criteria along with perfecting of physical and technical characteristics of the ionizing radiation sources are required. **Aim:** To study the effect of ¹⁹²Ir radiation on the chromosomal aberrations and prooxidant/antioxidant status of blood lymphocytes in gynecological cancer patients. **Materials and Methods:** The patients (n = 45) with endometrial, cervical and secondary cancer of vagina were enrolled in the study. For brachytherapy, the irradiation of vaginal mucosa was conducted using “GammaMed plus” device for contact radiation therapy with ¹⁹²Ir source. Prior to irradiation and in 20–24 h after brachytherapy session, the venous blood samples were obtained and peripheral blood lymphocytes (PBL) were cultured for cytogenetic analysis. The prooxidant/antioxidant status was determined in hemolysates by the method of hydrogen peroxide-induced chemiluminescence. **Results:** The average level of spontaneous chromosome aberrations in PBL of the patients was (7.8 ± 0.4) per 100 metaphases, which is more than twice higher than the upper limit of the average population values. The frequency of chromosome aberrations in PBL of patients after brachytherapy session was (15.3 ± 1.0) per 100 metaphases. An increased intensity of O₂^{•-} generation by PBL after brachytherapy session was also noticed. **Conclusion:** Local irradiation at a dose of 6 Gy featuring the first dose fraction of brachytherapy induces extra chromosomal aberrations in PBL of gynecological cancer patients and intensifies prooxidant processes in the blood.

Key Words: high-energy high-dose-rate brachytherapy, ¹⁹²Ir high-dose-rate sources, peripheral blood lymphocytes, cytogenetic analysis, radiation-induced chromosome aberrations.

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The experience of clinical application of ionizing radiation (IR) in oncology has convincingly proved the need for radiotherapy (RT) in the treatment of malignant neoplasms. Today, the advances in technology of RT application in cancer treatment has got to a completely new level and allow to significantly expand its indications. Over more than a hundred years of the use of various IR sources as a treatment tool, the radiobiology has emerged and developed in parallel as a new branch of science. Just the radiobiological studies have helped to clarify the onset of side problems from healthy tissues of the body that have arisen as a result of radiation exposure. Since then the qualitative changes have taken place and nowadays the impact of IR can be explained radiobiologically not only on the whole organism, its system or a single organ, but also at the genetic level [1–3].

Adverse radiation reactions, both general and local, are inherent in RT of cancer. Occurrence and degree of these reactions depend on individual radiosensitivity of the patient, energy characteristics of the IR source, magnitude and features of its distribution in the irradiated volume, methods and quality of RT, as well as the

period upon radiation treatment [4]. Severity of radiation reactions depends on the absorbed dose, its distribution over time, as well as a volume of irradiated tissues and their tolerance to IR. Grade of radiation reactions can be dramatically reduced by adhering to the rational principles of RT [5].

Expansion of radiobiological knowledge about genetic, biochemical and other pathways of pathogenesis of radiation damage can contribute to the development of more adequate tests that will reasonably predict the severity of radiation injury to healthy tissues in tumor environment [1, 6].

Current treatment of gynecological cancer patients involves a range of methods among which the brachytherapy or intracavitary RT using ¹⁹²Ir radiation sources hold high positions. A relatively low average energy of gamma radiation (0.38 MeV) is the main advantage of these sources. In addition, the higher specific activity of ¹⁹²Ir (450 Ci/g) allows the use of smaller sources providing irradiation with a high dose rate (> 12 Gy/g). Given that the half-life of ¹⁹²Ir is 22 times shorter than ⁶⁰Co, it can be used in a fractional irradiation. The advantage of brachytherapy is that a dose of radiation is applied directly to the tumor, which is difficult to achieve with external-beam RT [7]. The use of automated applicator delivery systems under computer control allows performing the intracavitary RT in the mode of high

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Abbreviations used: IR – ionizing radiation; PAR – prooxidant/antioxidant ratio; PBL – peripheral blood lymphocytes; RT – radiotherapy.

dose rate [8]. It should also be noted that experimental studies to determine the characteristics of RT regimens on laboratory animals are technically challenging [9]. Performing the bioindication of radiation injuries as a model for radiobiological research, which meets the requirements of the United Nations Scientific Committee on the Effects of Atomic Radiation, World Health Organization and International Atomic Energy Agency, it is most appropriate to use a culture of human peripheral blood lymphocytes (PBL) [10].

Under therapeutic irradiation the radiation-induced apoptosis of lymphocytes and, as a consequence, devastation of lymphoid organs and onset of lymphopenia occur at an early stage in the body of patients [1]. Given that the growth of tumors of different genesis is accompanied by the development of profound disorders in immune system, the extra radiation exposure enhances immunosuppression and may contribute to emergence of secondary tumors of radiation origin [3]. The radiobiological support of RT could be based on bioindication of chromosomal radiation damage in the lymphocytes from the circulating pool of patient's blood as highly radiosensitive cells from tumor environment. In addition, the study of blood biochemical parameters, namely the pro/antioxidant ratio distortion and intensity of superoxide anion radical (O_2^-) generation indicates the oxidative stress in the patient, which precedes development of genome instability that we discussed earlier [11]. The analysis at the chromosomal level makes it possible to assess the radiation-induced genome instability in non-malignant cells that fall into the area of therapeutic irradiation.

Given the above, the aim of the study was to study the effect of ^{192}Ir radiation on the chromosomal aberrations and prooxidant/antioxidant status of PBL in gynecological cancer patients. This could be advantageous for predicting the radiation complications based on biological effects of the ^{192}Ir source of IR in further studies.

MATERIALS AND METHODS

Patients and RT. The research was conducted at the Radiation Oncology Department of the National Cancer Institute of the Ministry of Health of Ukraine in accordance with provisions of the Declaration of Helsinki developed by the World Medical Association (2018). The informed consent of the patients to participate in the study was provided. The patients with $T_{1-2}N_0M_0$ stage cancer ($n = 45$, in particular, endometrial cancer ($n = 21$), cervical cancer ($n = 18$), and secondary cancer of vagina ($n = 6$)) were enrolled in the study that included examination and radiation treatment. Some patients ($n = 28$) had a burdened radiation history due to exposure after the Chornobyl NPP accident because of temporary or permanent residence in radiologically contaminated areas. The mean age of patients was (57.3 ± 5.2) years. Patients were diagnosed with stage II disease. According to the morphological structure, the glandular cancer of various differentiation grade was diagnosed in 73.6%

of patients and the squamous cell carcinoma in the rest of cases (26.4%). The latter are considered more sensitive to IR. Tumors in vagina represented the relapses in cervical stump with a spread to vaginal walls in the majority of patients ($n = 9$) with initially diagnosed cervical cancer. Tumors on the vaginal walls of various sizes and numbers occurred in the rest of patients having cervical cancer or uterine corpus cancer. There was a history of surgery and, if necessary, antitumor therapy (chemotherapy and/or RT) in these patients. Patients with the uterine corpus cancer ($n = 21$) had undergone surgery followed by brachytherapy of vagina. In this group, the cytogenetic study before administration of antitumor therapy was conducted.

After determining the boundaries of the tumor, the state of critical organs, the presence/absence of concomitant pathology and morphological identification of the tumor, the correct planning of conservative treatment of patients was initiated. GammaMed plus device was used for contact radiation therapy with ^{192}Ir source. Single boost dose of 6.0 Gy to a depth of 0.5 cm from the surface of the vaginal mucosa was delivered consequently up to a total boost dose of 24.0 Gy. Prior to irradiation and in 20–24 h upon the brachytherapy session, the venous blood sampling for radiobiological tests was applied. Topometric preparation before brachytherapy session included triple contrast enhancement (bladder, vagina and rectum) using "Eclipse" (Varian Medical Systems, USA) planning system to plan the dose delivery based on the images obtained by X-ray apparatus equipped with C-arc comprising a part of a complex for high-activity source intracavitary brachytherapy.

For planning the external beam RT, the doses of the previous RT were taken into account. The conformal external beam RT was administered using "Clinac 2100 CD" linear electron accelerator (Varian Medical Systems, USA) with mandatory pre-radiation 3D topometric preparation on a computer tomograph with a function of virtual simulation using the "Eclipse" computer planning system and generation of the three-dimensional model of patient. For external beam RT single boost dose of 1.8–2.0 Gy was delivered to the tumor bed and regional metastasis zone with a total boost dose of 42–46 Gy.

Cytogenetic studies. Peripheral blood from the stage II primary patients before and after first fraction of brachytherapy ($n = 21$) and healthy donors (control group, $n = 15$) was collected in the standard sterile Vacutainer tubes with Li-heparin anticoagulant. PBL culture and metaphase analysis of chromosome aberrations were performed according to the international standard protocol [12] with some modifications. Phytohemagglutinin (PHA) was used as a mitogen, which stimulates only T-lymphocytes to divide. Proliferative potential of PHA-stimulated lymphocytes was determined by calculating the mitotic index of cells as an additional indicator.

Biochemical studies. The prooxidant/antioxidant ratio (PAR) was determined in hemolysates by the method of hydrogen peroxide-induced chemilumi-

nescence [13]. The intensity of O₂^{•-} generation by PBL was estimated by CL method using lucigenin indicator, which reacting with O₂^{•-} illuminates the light quanta [14]. The data were expressed in pulses per 180 s. Measurements were performed on the “AutoLumat LB 953” unit (Berthold, Germany).

Statistical analysis. Statistical analysis was performed using Mann — Whitney test. Data are presented as M ± SE, where M is the mean value; SE is the standard error of the mean value. Differences were considered statistically significant when *p*-values were less than 0.05.

RESULTS AND DISCUSSION

Analysis of RT toxicity was performed according to the RTOG/EORTC classification (1995) [15]. Toxic effects of the treatment did not exceed grade II. General toxicity is manifested by a slight nausea observed in the vast majority of patients in both groups during treatment, which required no medical correction. Neither significant neutropenia nor thrombocytopenia were observed. The condition of patients had normalized in 3–4 weeks after treatment completion. No manifestations of the late general toxicity were observed in any patient at examination up to 6 months after treatment. There were almost no local radiation reactions of grade II. Local mucositis grade I of the upper third of vagina in a form of mucosal hyperemia was observed in the vast majority of patients. Membrane epitheliitis of vagina (grade II toxicity) was somewhat more common in the patients with a burdened radiation history. Vaginal sanitation with antibacterial drugs was applied during treatment, which allowed continuing the course of RT until its completion. Early grade I and II radiation cystitis was observed mainly in elderly women and in patients with chronic comorbidities. No early radiation rectitis of grade II in the course of combined RT was revealed. Exacerbations of chronic hemorrhoids and/or enterocolitis, which rarely developed on the background of conformal RT, were mainly noted. An increase in the number and manifestations of local rectal toxicity was observed in diabetic patients.

Late erosive cystitis was diagnosed 3 months upon treatment in 4.5% of patients in the group of subjects with a burdened radiation history. Signs of erosive radiation proctitis were detected in 6.7% of patients from the same group who lived in radiologically contaminated areas. No significant differences in manifestations and frequency of the late radiation reactions were revealed in the studied patients for 6 months of the outpatient follow-up.

Value of the spontaneous level of chromosome aberrations is a necessary characteristic to assess the effect of ¹⁹²Ir IR source on cellular genetic instability. Low and relatively constant spontaneous level of aberrations in PBL of the almost healthy individuals and at the same time high radiosensitivity of chromosomes in comparison with chromosomes of other cells in human body allows to reliably registering an increase of the induced aberrations above spontaneous level. It is known from

the literature and from our own research that the frequency of spontaneous chromosome aberrations can range within 0–3% of aberrations with predominance of chromatide type fragments [6]. Nevertheless, this figure may vary under the influence of external and internal factors, including medical and biological features of the study group. An increased level of DNA damage in PBL is often observed in cancer patients. According to our research, the average level of spontaneous chromosome aberrations in the group of primary gynecological cancer patients was (7.8 ± 0.4) per 100 metaphases (Table), which is more than twice higher than the upper limit of the average population values. Individual fluctuations of the parameter ranged from 5 to 10 aberrations per 100 metaphases. We calculated that one aberrant cell contained 1.04 aberrations. Chromatid-type aberrations significantly prevailed in the spectrum of registered rearrangements. Deletions accounted for 66% of the total number of chromatid aberrations (Fig. 1). The chromatid gaps found in PBL of primary gynecological cancer patients may be considered as a predictor of genome instability in these cells.

Table. Cytogenetic parameters of blood lymphocytes in primary gynecological cancer patients prior to RT and upon the first brachytherapy fraction applied

Cytogenetic parameter per 100 metaphases	Mean group value ± SE	
	Prior to RT	After the first brachytherapy fraction
Aberrant metaphases, %	7.5 ± 0.4	14.7 ± 1.0*
Total frequency of chromosome aberrations	7.8 ± 0.4	15.3 ± 1.0*
Total chromatide-type aberrations	5.7 ± 0.5	8.8 ± 0.9*
Deletions	3.8 ± 0.4	5.5 ± 0.7*
Isodeletions	0.15 ± 0.37	0.3 ± 0.2
Chromatid exchanges	1.7 ± 0.3	3.0 ± 0.7*
Total chromosome-type aberrations	2.0 ± 0.4	6.4 ± 0.7*
Paired fragments	1.6 ± 0.3	3.3 ± 0.4
Dicentric chromosomes	0.15 ± 0.12	2.1 ± 0.3*
Ring chromosomes	0.23 ± 0.14	0.1 ± 0.1
Points and acentric rings	0.07 ± 0.07	0.9 ± 0.3*
Abnormal chromosomes	0	0.2 ± 0.1*

Note: * difference is significant compared to the values prior to RT (*p* < 0.05).

Thus, the total frequency of chromosomal aberrations in PBL of patients before RT exceeds the average population value due to aberrations of the chromatid type. The increase in the spontaneous level of structural rearrangements in PBL of patients may indicate the genome instability due to carcinogenesis as a source of oxidative stress [11] and low efficiency of repair processes in normal tissue cells in the tumor environment [16]. According to contemporary views, the chromosomal instability of non-malignant cells in cancer patients is associated with fragments of tumor DNA, which circulates freely in the blood of patients, i.e.



Fig. 1. Microphotograph of metaphase plate from PBL of primary patient before irradiation. Deletion is indicated by an arrow

with the so-called “bystander effect” [17]. It is also necessary to take into account the role of intoxication of the patient’s body, which accompanies the cancer process. This may increase the sensitivity of normal cell genome to the action of various damaging agents.

Frequency and spectrum of chromosome aberrations primarily determined in patients’ PBL allowed us to assess the effect of ^{192}Ir radiation on chromosomal instability in these cells after the first fraction of therapeutic irradiation. A total frequency of chromosome aberrations in the irradiated *in vivo* PBL of patients was (15.3 ± 1.0) per 100 metaphases (Table). Individual values ranged from 11 to 21 aberrations per 100 metaphases. In contrast to the spontaneous level, an intensive rate of formation of the chromosome-type aberrations was recorded after local irradiation of patients, namely the radiation markers including dicentrics, rings, paired fragments, and abnormal chromosomes, specifically (5.7 ± 0.7) aberrations per 100 metaphases. The obtained data indicate a key role of chromosomal type aberrations in the formation of ^{192}Ir -induced genome instability of non-malignant cells in the tumor environment. The distribution of aberrations per each aberrant cell (1.04 aberrations per 1 aberrant cell) did not depend on the action of ^{192}Ir . This means the increase of number of aberrant cells, rather than of their load due to local irradiation of a patient at a dose of 6.0 Gy.

According to contemporary views, the cellular radiosensitivity and radiosensitivity of the body as a whole are largely determined by their reparative potential, which is closely linked to the immune system. Disorders in the genome stability and balance are an important part of carcinogenesis and occur against the background of immunosuppression [18].

In our study, the mitotic index of PBL decreased by 1.84 times after the first fraction of ^{192}Ir -irradiation delivered to the patients. Obtained data correspond to the basic provisions of classical radiobiology, reflecting the radiation-induced immunosuppression of “indicator” cells (Fig. 2).

The wide interindividual variability of the spontaneous PAR level from (8.53 ± 1.4) to (17.92 ± 0.39) thousand pulses per 180 s was detected in hemolysates obtained from gynecological cancer patients. The average PAR

value (11.53 ± 0.87) thousand pulses per 180 s was by 33% lower than that obtained in the blood of healthy donors in our previous study [19]. Such data indicate the activation of antioxidant defense systems in response to the development of cancer. After the first fraction of ^{192}Ir -irradiation (6.0 Gy), the PAR value varied in the range of 6.04–19.37 thousand pulses per 180 s. Average PAR value increased by 28% ($p < 0.05$) indicating the intensification in prooxydative processes in the blood of patients. Average value of the intensity of O_2^- generation by lymphocytes in the blood of patients was (565.4 ± 33.9) pulses per 72 s corresponding to the normal values. After local ^{192}Ir irradiation (6.0 Gy dose) there was an increased intensity of O_2^- generation by lymphocytes by 21%, specifically (685.2 ± 70.5) pulses per 72 s, which might indicate a decrease in antioxidant activity or depletion of its potential due to irradiation.

Summarizing the results, it was found that PBL of patients prior to the beginning of ^{192}Ir -RT were already characterized by abnormal PAR processes and genome instability. Local irradiation at a dose of 6 Gy featuring the first dose fraction has lead to the further aggravation of genome instability due to the induction of chromosomal aberrations and amplified PAR processes in the blood, which are an integral indicator of intensity of the free radical processes. Such changes in cells of the tumor environment can lead to the development of distant radiation complications, including secondary tumors of radiation etiology. The latter dictates a need to find and use the radiomitigators accelerating the repair process only in normal cells in the tumor environment.

The results of our clinical study showed a clear trend to increased grade and number of radiation reactions upon irradiation with a ^{192}Ir source in patients with a burdened radiation history.

The thorough examination of gynecological cancer patients with involvement of radiobiological indicators of highly radiosensitive blood cells provides an opportunity to predict the likelihood of radiation reactions and prevent their development in a timely manner. The development of more powerful fundamental and clinical radiobiological basis should be beneficial in search of new approaches for enhancing tumor radiosensitivity with accompanying increase in radioresistance of healthy tissues.

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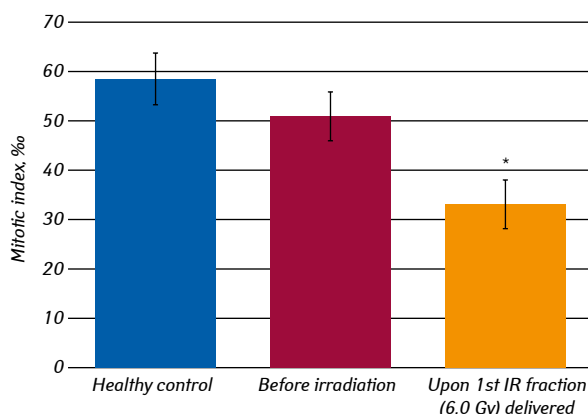


Fig. 2. Mitotic activity of PBL in healthy donors and cancer patients before and upon irradiation: *difference is significant compared to the values prior to RT ($p < 0.05$)

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ВПЛИВ БРАХІТЕРАПІЇ НА ЦИТОГЕНЕТИЧНІ ПАРАМЕТРИ ТА ОКИСНИЙ СТАТУС ЛІМФОЦИТІВ ПЕРИФЕРИЧНОЇ КРОВІ ХВОРИХ ЗІ ЗЛОЯКІСНИМИ НОВОУТВОРЕННЯМИ ГІНЕКОЛОГІЧНОЇ СФЕРИ

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Стан питання: Найсучасніші технології брахітерапії з високкодозними джерелами ^{60}Co та ^{192}Ir у сучасних протоколах лікування онкологічних хворих дозволяють досягти підведення максимальної дози до мішені, що становить клінічний інтерес, з мінімальним опроміненням навколишніх органів та тканин. Для мінімізації та подолання ранніх та пізніх радіаційних ускладнень необхідна розробка відповідних радіобіологічних критеріїв разом з удосконаленням фізико-технічних характеристик джерел іонізуючого випромінювання. **Мета:** Вивчити вплив опромінення ^{192}Ir на хромосомні аберації та прооксидантний/антиоксидантний стан лімфоцитів крові у хворих зі злоякісними новоутвореннями гінекологічної сфери. **Матеріали та методи:** У дослідження були включені пацієнти ($n = 45$) з раком ендометрію, шийки матки та його рецидивом у піхві. Курс брахітерапії передбачав опромінення слизової оболонки піхви за допомогою апарату “GammaMed plus” для контактної променевої терапії з джерелом ^{192}Ir . Зразки венозної крові та лімфоцити периферичної крові (ЛПК) для цитогенетичного аналізу були отримані перед опроміненням та через 20–24 год після сеансу брахітерапії. Прооксидантний/антиоксидантний статус визначали в гемолізатах методом хемілюмінесценції, індукованої перекисом водню. **Результати:** Середній рівень спонтанних хромосомних аберацій у ЛПК пацієнтів становив $(7,8 \pm 0,4)$ на 100 метафаз, що більш ніж удвічі перевищує верхню межу середніх значень популяції. Частота хромосомних аберацій у ЛПК пацієнтів після сеансу брахітерапії становила $(15,3 \pm 1,0)$ на 100 метафаз. Також було помічено підвищену інтенсивність генерації O_2^- у ЛПК після сеансу брахітерапії. **Висновок:** Локальне опромінення у дозі 6 Гр як перша дозова фракція брахітерапії викликає додаткові хромосомні аберації у ЛПК та посилює прооксидантні процеси в крові хворих зі злоякісними новоутвореннями гінекологічної сфери.

Ключові слова: високкодозна брахітерапія, високкодозні джерела ^{192}Ir , лімфоцити периферичної крові, цитогенетичний аналіз, радіаційно-індуковані хромосомні аберації.