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TOPICAL ASPECTS OF MODERN RADIATION ONCOLOGY

To the 65th anniversary of its foundation of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine

It has been established that radiation therapy along with devitalization of malignant neoplasms increases the risk of post-radiation complications from radio-vulnerable tissues and organs. Therefore, minimizing the frequency and severity of these complications after RT courses without compromising its effectiveness remains a pressing issue in modern oncology. An effective approach to treating oncogynecological patients is the introduction of chemotherapy in combination with RT into clinical practice. It is known that cellular DNA repair systems aimed at preserving and stabilizing the integrity of the genome counteract the death of neoplastic cells and thereby reduce the effectiveness of tumor radiation therapy. The author of this work proposed a new approach to improving cancer prevention aimed at reducing the risk of post-radiation complications. The main goal of the proposed methodology for tertiary cancer prevention is to increase the radioresistance of tissues surrounding the tumor. The article is aimed for the professionals who work in experimental and applied areas of radiobiology, oncology, radiation medicine and others.

Modern oncology has undergone significant changes due to the introduction of information and digital technologies, new algorithms for diagnosis and treatment of patients. However, it has not yet been possible to fully maintain the priorities of 'monotherapy' for socially significant oncological diseases, including locally advanced cervical cancer (CC) [1]. CC is a serious global health problem, ranking fourth among female cancers worldwide [2]. This fact is associated with the spread of the human papillomavirus [3, 4]. For a long time, radiation therapy (RT) was considered the standard treatment for this type of tumour. Currently, expensive multi-component treatment programs aimed at improving survival and quality of life are being developed and implemented for patients with CC. The use of brachytherapy (contact therapy) is a promising direction in the treatment of gynecological cancers, but its use is declining worldwide [5]. In the development of the standard RT method, the main factor limiting the dose of ionizing radiation was skin reactions, with the peak dose occurring in the area where the radiation beam entered. Despite the progress achieved in radiation oncology, due to the use of modern technology and conformal therapeutic irradiation strategies, early complications significantly affect the quality of life of patients. They can lead to the sequential late effects of radiation exposure [6]. The socio-economic factor—the cost of supportive therapeutic procedures-should also be taken into account. Additional adverse effects can exacerbate the severity of early complications of RT, such as the chemotherapeutic component. The combined use of radiation and chemotherapy significantly increases the effectiveness of the treatment and survival rates of cancer patients, especially in cases where RT is effective. In this case, therapeutic irradiation (remote and brachytherapy) is used for the primary tumor, and chemotherapy is used to reduce the spread of the cancer process.

Thus, along with reducing the risk of cancer recurrence, RT increases the risk of post-radiation complications in healthy tissues. Therefore, minimizing the frequency and severity of these complications after RT courses without compromising its effectiveness remains a pressing issue in modern oncology.

BIOLOGICAL (CYTOGENETIC) DOSIMETRY/INDICATION OF RADIATION DAMAGE

High rates of urbanization and industrialization lead to the deterioration in health, reproductive dysfunction, and intrauterine development in certain categories of the population. The active use of nuclear energy in various areas of human activity has led to the formation of cohorts of people exposed to excessive radiation. Bioindication of the degree of radiation damage using a radiation marker — the frequency of

chromosome-type aberrations — has shown that the problem of the influence of the low doses of ionizing radiation on the occurrence and development of radiogenic diseases remains relevant [7].

The radiation-induced damage of DNA can lead to cell death, the formation of chromosome aberrations, genotoxicity, and other mutational events, including carcinogenesis. The use of a human blood lymphocyte test system is recognized by international organizations such as the WHO, IAEA, UNSCEAR, and others as the 'gold standard' for biodosimetry of radiation damage and allows modelling increased radiosensitivity in the human body [8, 9]. This method also provides for information about previous radiation exposure. In this case, it is necessary to be guided by the provisions of the World Medical Association's Declaration of Helsinki, which provides for the informed consent of the patient, adopted at the First National Congress of Ukraine on Bioethics in 2001. Researchers have concluded that the retrospective cytogenetic analysis is advisable for medical and social assessment if, for various reasons, physical dosimetry was not performed in the early post-radiation period [10]. In addition, the use of cytogenetic test in preclinical studies in the field of radiation oncology allows us to determine the optimal conditions for the manifestation of the protective properties of radioprotectors with the calculation of the coefficient of modification of the radiation effect.

CHEMORADIOTHERAPY

Along with surgical intervention, RT has always been considered the most effective method of treating patients with locally advanced CC. Progression of the disease in the pelvic area is a common cause of death in patients with parametrial infiltrates and metastatic involvement of regional lymph nodes. An effective approach to treating patients with CC is the introduction of chemotherapy in combination with RT into clinical practice [11, 12].

It has been established that cisplatin, bleomycin, doxorubicin, and others inhibit the repair of radiation-induced chromosome damage by affecting its enzymes [13]. It is known that cellular DNA repair systems aimed at preserving and stabilizing the integrity of the genome counteract the death of neoplastic cells and thereby reduce the effectiveness of tumor RT. Therefore, an urgent task in radiation oncology is to find ways to inhibit repair processes in tumor cells while preserving their activity in normal (non-malignant) cells.

Like ionizing radiation (IR), chemotherapeutic agents can induce DNA damage in the form of breaks. For example, cisplatin exposure is associated with an increase in the level of single-strand breaks (SSBs) in DNA induced by irradiation. Inhibition of repair processes and the conversion of SSBs into double-strand breaks (DSBs) leads to an enhancement of the radiobiological effect, especially in fractionated rather than single-dose regimens. It should be emphasized that in order to achieve therapeutic benefit, it is necessary to select drugs that have an affinity for the tumor. This will protect the healthy tissues surrounding the tumor. The following types of radiation protection of healthy tissues are distinguished:

- *preventive* — before irradiation;
- *attenuating* — at the time of or immediately after irradiation, before the onset of clinical symptoms;
- *therapeutic* — during the phase of clinical symptom manifestation.

A topical issue in chemoradiotherapy is an increase in early toxicity. For example, when using cisplatin, early effects include complications from the digestive tract, while late effects include kidney dysfunction. In general, early chemical toxicity manifests itself in rapidly renewing tissues, while late toxicity manifests itself after a latent period of several months to several years. Late effects are irreversible. The pathogenesis of late effects of radiation is associated with cell death, differentiation of fibroblasts and vascular endothelial cells (loss of the capillary network). All these cells communicate with each other through cytokines and growth factors. This leads to the loss of functional activity of the irradiated tissue volume or organ. The manifestation of late effects depends on the radiation dose. With increasing observation time, the dose curve shifts to the low dose range.

If weekly examinations of patients are necessary for 3 months to detect signs of early effects of radiation on healthy tissues surrounding the tumor, then late effects should be examined every few months after radiation.

The highest risk of developing late toxicity increases when drugs have selective toxicity for tissues within the irradiated volume. This is inherent in bleomycin, which exhibits pulmonary toxicity, and cisplatin, which affects kidney function, among others. Therefore, it is logical not to prescribe bleomycin for mediastinal tumors. Thus, it should be noted that "late toxic effects in healthy tissues are enhanced by inhibition of DNA repair and by the mechanism of drug toxicity to sensitive tissues" [12].

Just like radiation, some chemotherapeutic drugs can damage DNA by causing breaks, adducts, and intercalations. For example, cisplatin makes more SSBs and turns radiation-induced SSBs into DSBs. It is the inhibition of repair processes or the conversion of SSBs into DSBs that leads to an increase in the radiobiological effect. Moreover, a number of studies have shown that the repair of damaged DNA in tumor cells can occur more actively than in non-malignant cells [14–16]. In this case, a therapeutic advantage will be obtained if drugs with tumor tropism are used. Since most chemotherapeutic drugs are cell division inhibitors, they are most effective on proliferating cells. For example, methotrexate is an inhibitor of enzymes involved in

DNA synthesis and S-phase cell repair. The strongest potentiation of the radiobiological effect occurs in the case of the cell cycle synchronization when cells are in the highly radiosensitive G2 period [17].

The effectiveness of RT in most cases is determined by the degree of difference in the radiosensitivity of tumor and normal cells, known as the 'therapeutic sensitivity interval'. These differences are due to the varying severity of recovery processes from post-radiation damage, which are more pronounced in normal tissues surrounding the tumor. The response of tissues to irradiation depends on their initial radiosensitivity, the concentration of oxygen in the irradiation zone, and the number of dividing cells. Any of these factors can modify the radiation response of a tumor, which must be taken into account in further studies on the effects of these factors on non-malignant cells.

RADIOMODIFIERS

Thanks to advances in radiobiology, a specific strategy has been developed for the influence of radiomodifying agents of a physical and chemical nature on the radiosensitivity of both normal and tumor cells. An important factor here is the preferential accumulation of radiomodifiers in target tissues. The implementation of targeted changes in radiosensitivity, both to enhance tumor damage and to protect normal tissues in its surrounding area, is one of the key issues in radiation oncology with a view to improving its effectiveness [18–20]. The development of means of modifying the effects of radiation on healthy tissues should be based on knowledge of the processes underlying these effects: from the formation of free radicals to late changes in irradiated tissues. The formation of free radicals is one of the early events that occur in a cell during irradiation. Therefore, the introduction of free radical trap agents or stimulation of endogenous mechanisms for their detoxification leads to a reduction in damage to biologically important molecules and, ultimately, to the degree of the manifestation of radiation effects at the cellular and tissue levels. Thus, the formation of free radicals is one of the important events occurring in the cell during irradiation. One of the most well-known drugs that act as a radical trap is amifostine [21, 22]. Amifostine is an organic compound from the group of thiophosphorus derivatives, which was introduced in 2007 to reduce the effects of radiation on various healthy tissues [22]. However, when this radioprotector is taken orally, there are some serious side effects, like nausea, high blood pressure, and skin reactions. Literature data on the effect of this radioprotector on tumors are contradictory. Therefore, in accordance with the paradigms of evidence-based medicine, in order to achieve maximum therapeutic benefit, it is necessary to compare its effects with the effects of traditional protectors on tumors, in the setting of irradiation in the low (above background) dose range [12, 23].

CONCLUSION

Analysis of literature data and the experience of foreign and Ukrainian researchers indicates that the protection of nonmalignant tissues surrounding the irradiated tumor remains a key issue in modern radiation oncology, given the increased risk of early and late radiation complications. Radiation complications require long-term and costly treatment, which hinders the improvement of the effectiveness of therapeutic irradiation. Such consequences of radiation therapy for cancer patients lead to psychological and economic problems not only in the patient's family, but also in society as a whole. We see a new approach to address this issue in improving tertiary prevention (reducing the incidence and severity of post-radiation complications) of cancer, which consists of the vectors we propose. The first 'biodosimetric' vector is key, which involves the identification of biomarkers that depend on the amount of radiation exposure. To identify and justify predictors of radiosensitivity of cells from the cancer environment, we used a wide range of radiobiological indicators focusing on some aspects of the pathogenesis of complications. The selection of predictive biomarkers was based on the construction and analysis of classical dose-effect relationships during test irradiation in a wide range of doses using linear and linear-quadratic mathematical models, as well as the response to the action of ionizing radiation in low doses. This made it possible to differentiate the effects of low doses from intact control values. The second vector is 'radiosensitive,' which involves determining the interindividual variability of predictors in the therapeutic irradiation of gynecological cancer patients. The third vector is 'radioresistant' — experimental justification for the use of a radioprotector to enhance the radioresistance of critical healthy cells from the tumor environment. The results obtained are recommended to be implemented in the concept of personalized prevention of radiation complications following radiation therapy in cancer patients.

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АКТУАЛЬНІ АСПЕКТИ СУЧАСНОЇ РАДІАЦІЙНОЇ ОНКОЛОГІЇ

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Резюме. *Променева терапія разом із девіталізацією злоякісних новоутворень підвищує ризик пострадіаційних ускладнень з боку радіочутливих тканин та органів. Тому мінімізація частоти та тяжкості цих ускладнень після курсів променевої терапії без шкоди для її ефективності залишається актуальним питанням у сучасній онкології. Ефективним підходом до лікування онкогінекологічних пацієнтів є впровадження хіміотерапії в поєднанні з променевою терапією в клінічну практику. Відомо, що клітинні системи репарації ДНК, спрямовані на збереження та стабілізацію цілісності геному, протидіють загибелі неопластичних клітин і, тим самим, знижують ефективність променевої терапії пухлини. Запропонований новий підхід до покращення профілактики раку, спрямований на зниження ризику пострадіаційних ускладнень. Основною метою запропонованої методології третинної профілактики раку є підвищення радіорезистентності тканин, що оточують пухлину. Стаття призначена для фахівців, які працюють в експериментальних та прикладних галузях радіобіології, онкології, радіаційної медицини та інших.*

Ключові слова: терапевтичне опромінення, пострадіаційні ускладнення, репарація, токсичність, радіомодифікатори

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