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ВАРИАНТ ПРОФИЛАКТИКИ ЛУЧЕВОГО ЦИСТИТА
ВАРІАНТ ПРОФІЛАКТИКИ ПРОМЕНЕВОГО ЦИСТИТУ
OPTION TO PREVENT RADIATION CYSTITIS

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Ключевые слова: рак мочевого пузыря, антиоксиданты, дистанционная гамма-терапия, лучевые реакции, лучевые повреждения, цистит

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Key words: bladder cancer, antioxidants, remote gamma therapy, radiation reactions, radiation injury, cystitis

Анотация

ВАРИАНТ ПРОФИЛАКТИКИ ЛУЧЕВОГО ЦИСТИТА

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Дистанционная лучевая терапия (ДПТ) является эффективным методом лечения для многих видов новообразований. Но при различных подходах, полях и комбинациях доз лучевые поражения мочевого пузыря неизбежны. Поэтому одним из приоритетных вопросов в современной радиологии – это предупреждение и борьба с лучевыми реакциями и повреждениями. Целью работы стала разработка способа

профилактики и лечения лучевых реакций при лечении больных раком мочевого пузыря, у больных которые получают дистанционную гамма-терапию (ДГТ) и обоснование антиоксидантной и репарационной роли препарата «Эмоксипин» при данной патологии. Изучалась выраженность лучевых реакций у больных, получавших лучевое лечение в режиме обычного фракционирования и при мультифракционировании дозы. В наблюдении принимало участие 27 больных с диагнозом рак мочевого пузыря и которым проводили ДПТ по радикальной программе. Анализируя полученные результаты, можно отметить, что применение ДПТ в режиме мультифракционирования дневной дозы достоверно ($p = 0,05$) снижает лучевые реакции слизистой мочевого пузыря. Так, реакции 3 степени (язвенные) различаются в 4,31 раза в пользу ИИ (опытной) группы где использовали режим мультифракционирования и заливки препарата «Эмоксипин». Реакции 2 степени (эрозивно-дескваматозные) отличаются в 1,24 раза и также говорят в пользу II группы, но этот показатель не достоверен. Реакции 1 степени (катаральные) отличаются в 3,72 раза, что имеет достаточную вероятность в пользу лечения проведенного во II группе больных.

Действие инсталляций мочевого пузыря у больных с лучевыми циститами, отягощенные инфекционным процессом, по сравнению с традиционными методами терапии позволило сократить время пребывания больных в стационаре на 6-7 дней.

Анотація

ВАРІАНТ ПРОФІЛАКТИКИ ПРОМЕНЕВОГО ЦИСТИТУ

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Ключові слова: рак сечового міхура, антиоксиданти, дистанційна гамма-терапія, променеві реакції, променеві ураження, цистит

Дистанційна променева терапія (ДПТ) є ефективним методом лікування для багатьох видів новоутворень. Але при різних підходах, полях та комбінаціях доз променеві ураження сечового міхура неминучі. Тому одним з пріоритетних

невирішених питань у сучасній радіології є питання попередження та боротьби з променевими реакціями та ушкодженнями. Ціллю роботи стала розробка способу профілактики та лікування променевих реакцій при лікуванні хворих на рак сечового міхура, що отримують дистанційну гамма-терапію (ДГТ) та обґрунтування антиоксидантної і репараційної ролі препарату «Емоксипін» при даній патології. Вивчалась вираженість променевих реакцій у хворих, які отримували променеве лікування в режимі звичайного фракціонування та при мультифракціюванні дози. У спостереженні приймало участь 27 хворих з діагнозом рак сечового міхура і яким проводили ДПТ по радикальній програмі. Аналізуючи отримані результати, можна відзначити, що застосування ДПТ в режимі мультифракціювання денної дози вірогідно ($p=0,05$) знижує променеві реакції слизової сечового міхура. Так, реакції 3 ступеню (виразкові) різняться в 4,31 рази на користь II (дослідної) групи де використовували режим мультифракціювання та заливки препарату «Емоксипін». Реакції 2 ступеню (ерозивно-десквамативні) різняться в 1,24 рази і також говорять на користь II групи, але цей показник не вірогідний. Реакції 1 ступеню (катаральні) різняться в 3,72 рази, що має достатню вірогідність на користь лікування проведеного в II групі хворих.

Дія інсталяцій сечового міхура у хворих з променевими циститами, що обтяжені інфекційним процесом, в порівнянні з традиційними методами терапії дозволило скоротити час перебування хворих у стаціонарі на 6-7 днів.

External Beam Radiation Therapy (EBRT) is an efficient method of treatment for many types of tumors. But with different approaches, fields, and combinations of doses, the bladder lesions are inevitable. Therefore, one of the priority unsolved issues in the present day radiology is the issue of prevention and control of radiation reactions and injuries. The purpose of the present study was to develop a method for the prevention and treatment of radiation reactions in the treatment of patients with bladder cancer receiving gamma-ray teletherapy (GRT) and to substantiate the antioxidant and reparative role of the Emoxypin drug in this pathology.

The severity of radiation reactions in patients receiving radiation therapy in the usual fractionation mode and with multi-fractionation of dose was under study. The total of 27 patients participated in the observation, those with bladder cancer diagnosed and subjected to the EBRT on the definitive treatment program. Analyzing the results obtained, it can be noted that the use of EBRT in the mode of the daily dose multifraction reliably ($p = 0.05$) reduces the reaction of the bladder mucosa. Thus, the reactions of the 3rd degree (ulcerative) differ by 4.31 times in favor of group II (experimental) where the mode of multifraction and the Emoxypin drug was used. Reactions of the 2nd degree (erosive-desquamated) differ by 1.24 times and also favor group II, but this indicator is unreliable. Reactions of 1 degree (catarrhal) differ by 3.72 times, which has a sufficient reliability in favor of the treatment performed in the patients of group II.

The effect of bladder installations in patients with radiation cystitis, complicated with an infectious process, compared with the traditional methods of therapy, permitted to reduce the term of patients' stay in hospital by 6-7 days.

Introduction. External Beam Radiation Therapy (EBRT) is an efficient method of treatment for many types of tumors. In addition, it provides long-term survival without relapses and other manifestations of the disease. The purpose of performing radiation therapy is to bring a dose having a destructive effect to the tumor cell. At the same time, it is necessary to ensure the protection of healthy tissues, to the extent possible, in accordance with the laws of radiobiology and radiation physics [14]. The severe effects of irradiation, distant radiation injuries, are, unfortunately, part of the EBRT. Effective treatment can be obtained through the skill and the use of modern technologies with the persistent prevention of radiation reactions [10, 12, 14].

Any damage to the tissues of the small pelvis organs (bladder, rectum, endopelvic cellular tissue), whether it could be chemical, mechanical or physical (in this case, radiant) injury, leads to radiation injuries and to formation of scar tissue [6, 9, 10].

Analysis of current literature has shown that the number of papers devoted to this pathology in the domestic and foreign publications is insignificant and, as a rule, they have

the descriptive nature. In addition, methods for preventing radiation injuries are studied insufficiently, as well as rehabilitation issues and the life quality of the indoor patients in the postexposure periods [9, 12, 15]. Assessing the existing methods for treating radiation injuries of the pelvic organs that are presented in periodicals it can be stated that the results of diagnosing and treatment of such radiation lesions are unsatisfactory, they are manifested by frequent relapses of cystitis and as a result cause deformation of the bladder; endopelvic radiation fibrosis, and development of the chronic renal failure [4, 5, 6].

Regulation of this process depends on many factors determined by the injury extent and by the duration of the wound process. Also, the presence of somatic factors, namely: reduced immunity, endocrinopathy, anemic complications, the presence of microflora, microcirculation disorders, etc., causes decrease in the processes of reparation and prolongation of healing periods and, consequently, deformation of the organ, reducing its physiological functions [7, 8, 11] .

One of the priority issues in the treatment of bladder cancer is EBRT, which can be aimed at different purposes, one of which is a definitive treatment performed when surgery is impossible [1, 4].

In Europe, radiotherapy is performed quite frequently for bladder tumors. For example, in the UK at the conventional radiation, the total boost dose (TBD) is brought to 50 – 60 Gy with a single boost dose (SBD) of 1.8 - 2,0 Gy [51, 52]. However, Harvard Medical School researchers believe that in the case of bladder cancer it is necessary to bring TBD to 55-65 Gy. In general, radiotherapy for bladder cancer is carried out in two stages: the first TBD 45-50 Gy with SBD 1.8-2.0 Gy for the entire bladder; the second stage is the direct irradiation of the primary tumor [3].

Radial reactions arise predominantly at the beginning of radiotherapy and bring significant suffering to the patient. Some authors [11, 15] observed bladder lesion in 20% of patients who received 70 Gy or more in 30% of the bladder, or in the irradiation zone in 15% of the bladder - 5% of acute lesions.

Others [12, 13] denote a sharp growth of acute radiation injuries if TBD 65 Gy is delivered to one-third of the bladder. Acute symptoms usually occur 1 month after the irradiation is complete. In addition, it should be borne in mind that persistent hematuria is in most cases well treated with antioxidants and antihypoxants [7, 8, 11].

According to B. Emami et al. [14], TBD 65 Gy and SBD 1.8-2.0 Gy delivered to the entire bladder give practically 7% of late lesions. They determined that TBD 80Gy is also tolerant if a third of the bladder is irradiated.

But L.B. Marcs et al. [14], according to the data of the literature sources analysis, determined that as far as late lesions are concerned, the dose delivered to the entire bladder should be 45 Gy.

Taking into account the progress of radiation therapy for bladder cancer, Princess Margaret Hospital staff estimates that TBD 50-60 Gy at a SBD of 1.8-2.0 Gy for the entire bladder is a tolerant dose for most patients, and the TBD 65-70 Gy is only tolerant for a part of the bladder [14]. At the same time, the opinion of the staff at the Department of Oncurology and Radiation Oncology of the Massachusetts General Hospital, Boston, is that, with a conventional fractionation, the dose tolerant for the whole bladder is the TBD 40-45 Gy [13, 14].

There are other treatment regimens having a large number of fractions at low single doses (hyperfractionation) and fewer fractions, but with higher single doses at a lower total boost dose (hypofractization) [3, 10].

When planning radiotherapy, it is necessary to take into account the features of the ratio between the bladder to the surrounding tissues. Subject to irradiation should be not only the tumor but the regional metastasis zones. The latter include the lymph nodes below the bifurcation: hypogastric, obturation, inner and outer iliac, perivesical, pelvic, presacral [10,14] zones.

When choosing the fields for irradiation of the bladder it is advisable to use recommendations [14] of the Radiation Therapy Oncology Group (RTOG). The front and rear opposite fields are applied, as well as the left and right lateral ones. The upper boundary

is for the opposite front-back fields of connection L5 with S1, the lower one is the lower edge of locking openings, the lateral boundary is 1 cm away from the pelvic ring. The lateral fields have their front boundary 2 cm forward from the bladder wall or 1 cm forward from the pubic bone, their back boundary is 2 cm back from the bladder wall or between the middle and the rear third of the rectum.

From the above, it can be seen that, with different approaches, the fields and combinations of doses, the bladder injuries are inevitable. Therefore, one of the priority unsolved problems in modern radiology is the issue of prevention and control of radiation reactions and injuries. The issues' topicality is due to the lack of a single algorithm for using drugs that actively and efficiently prevent this process.

The work is a fragment of the initiative preconceptual research study of the HSEE "Ukrainian Medical Stomatological Academy": "Development of methods for prevention and treatment of drug-induced lesions of internal organs", state registration No. 0115U001087). Term for execution is: from 02/2015 to 02/2020.

The novelty of the work is focusing the interest on the direct synthetic antioxidant drug "Emoxypin", which prognostically inhibits the reaction of free radical peroxide oxidation (FRPO) [2, 4, 5, 6].

The purpose of the present study was to develop a method for prevention and curing of radiation reactions in the treatment of patients with bladder cancer receiving remote gamma-ray therapy (RGRT) and to substantiate the antioxidant and reparative role of Emoxypin drug in this pathology. The purpose also included prevention of relapses due to the restoration of local hemodynamics.

Materials and methods. The standard schemes for conservative treatment of the bladder radiation reactions (Dimexidum, Palin, Canephron, Methyluracil suppositories, etc.), known as of today, do not take into account the general principle of the drugs effect on local radiation induced hypoxia, which is obviously the key link of the pathogenesis. The harmful factor is also the toxicity of drugs and the list of side effects that prevent their use.

The key role in the pathogenesis of hypoxic states is the activation of lipid peroxidation and membrane-damaging effects of free radicals. Therefore, the stabilization of cell membranes damaged under hypoxia is the major factor causing the interest to this drug. The assumption that application of antioxidants in various pathological states accompanied by hypoxia is efficient, has been proved experimentally by many researchers.

Thus, taking into account the above stated, the use of Emoxypin drug is explained by the fact that it is an inhibitor of free radical processes, antihypoxant, antioxidant. It reduces blood viscosity and aggregation of thrombocytes, increases the composition of cyclic nucleotides in tissues and thrombocytes, expresses fibrinolytic activity, reduces vascular permeability and the risk degree of hemorrhages.

The 5% Dimexidum solution was chosen as the control drug, which is classically used for the prevention and treatment of radiation reactions. Dimethyl sulfoxide has a specific feature of penetrating through biological membranes, thus realizing its specific effects, including anti-inflammatory, anti-pyretic, analgetic, antiseptic, moderate fibrinolytic effect. The preparation enhances drugs penetration through the mucous membranes (ability to transport).

The severity of radiation reactions in patients receiving radiation therapy in the usual fractionation and the dose multi-fractionation regimens was studied.

Both early and late reactions were assessed for each of these treatment methods on the part of the bladder mucosa manifestations, namely manifestations of radiation cystitis. Radiation cystitis is a specific set of symptoms caused by the bladder walls injury (primarily its mucous membranes) under the impact of ionizing radiation in doses from 60 Gy and higher at classical fractionation.

Radiation cystitis (catarrhal, erosive, desquamative and ulcerative) are manifested by frequent urges for urination, macrohematuria, severe pain along the urethra, pain in the bladder area. The clinical picture of the radiation cystitis is estimated by the degree of the bladder wall lesion and the development of erosive and destructive processes in the mucous membrane, association with infection and the occurrence of bleeding.

The severity of radiation cystitis is estimated according to the intensity of the urinary tract functional disorder, based on ultrasound investigation and cystoscopy data.

As of today, the fact that the frequency of radiation damage depends on the quality of radiation therapy planning and performance, the total boost dose and the fractionation mode is a certainty. It is important to select the safest regimen for surrounding tissues during the irradiation, which is provided with the help of precise individual topometry with the precise determining of the organs syntopy. Application of stimulants and other special devices for precise visualization of organs entering the radiation zone is performed by the computer and ultrasound topometry, which permits to significantly reduce the load on healthy tissues.

In the radiation cystitis pathogenesis the leading role is played by radiation damages of the bladder wall, the degree of which directly depends on the total absorbed dose amount, which exceeds the tolerance of the bladder tissues. Equally important is the related inflammatory process, and therefore the treatment of bladder lesion should include therapeutic measures aimed at the specified links of the pathogenetic chain.

Therefore, all patients received, in addition to the local treatment, the same type general treatment, which included antibacterial, anticoagulant, vasoactive, immunostimulating and symptomatic therapy.

The total of 27 patients diagnosed with bladder cancer participated in the observation and received EBRT according the definitive treatment program. The patients did not reliably differ in age, complaints, clinical parameters, disease stage, etc.

To perform the assigned task (to raise the efficacy of treatment for patients with radiation bladder lesions), the patients were blindly divided into the two groups:

The I group (gr.) (N = 13) (the control one): the patients received EBRT on the definitive program of classic fractionation with SBD 2.2 Gy to TBD 60 – 65 Gy in 2 stages with a three-week break. For the prevention and treatment of radiation reactions, 10% Dimexidum solution was infused into the bladder after the radiotherapy session 2 times a day for 12-15 days.

The II gr. (N = 14) (the experimental one): the patients received EBRT on the definitive program with fractionation of the daily dose of SBD 1.1 Gy + 1.1 Gy = 2.2 Gy to TBD 60 - 65 Gy in 2 stages with a three week break. For the prevention and treatment of radiation reactions, infusions of the Emoxypine solution were performed into the bladder after the radiotherapy session: the drug was administered into the bladder by 150 mg 2 times a day for 12-15 days.

Results of the study. The effect was assessed during the treatment period and the short-range radiation effect (after 3 weeks) was assessed after the EBRT completion. The patients' complains of pain when urinating, blood admixtures were taken into consideration. General urine analysis data: hematuria and leukocytosis, protein admixtures. The control was performed according to cystoscopy and ultrasound investigation data.

In patients of the both groups with catarrhal cystitis after treatment, normal urine values have grown by 36%, bacteriuria completely disappeared in 30% of patients. Concerning hematuria, positive dynamics was observed in all patients. According to ultrasound investigation, in more than 62% of the patients the bladder condition has improved. Significant results were observed in the same group's patients with complicated forms of cystitis: the bladder's capacity has grown, the urinations frequency has reduced, a subjective improvement was observed by all the patients. The positive dynamics was confirmed by the ultrasound investigation and cystoscopy more than in 42% of patients in this group.

In patients with erosion-desquamative and ulcerative cystitis, as a result of the treatment, the therapeutic efficacy analysis has shown its significant effect on the frequency of urinations. In all patients, the inflammatory reaction has reduced, and in 58% of patients with complicated forms of cystitis, leukocyturia reached its normal values; in 87% in 70% of patients, bacteriuria and macrohematuria, respectively, have disappeared completely. According to the cystoscopy data, till the end of treatment, hyperemia of the bladder mucosa (82.5%) and edema (85%) have reduced.

Ulcerative reactions in group I were detected in 8 (61,54%) patients versus 2 (14,28%) in group II.

Erosion-desquamative reactions did not reliably differ and were observed in 3 (23,07%) patients in group I against 4 (28,57%) patients in group II.

The catarrhal reactions observed in the groups were manifested as follows: in group I they were detected in 2 (15,38%) patients versus 8 (57,14%) in group II.

The results are presented in Tab. 1

Table 1

Frequency of Radiation Reactions in the Bladder Mucosa, Depending on the Type of Treatment

Radiation reactions localization	Group I (n = 13) (control) EBRT (classic fractionation) with Dimexidum instillations			Group 2 (n = 14) (experiment) EBRT (dose multi- fractionation) with Emoxypine instillations		
	Reaction type	Number of cases		Reaction type	Number of cases	
		abs.	(%)		abs.	(%)
Bladder mucosa	Catarrhal	2	15.38%	Catarrhal	8	57.14%
	Erosion-desquamative	3	23.07%	Erosion-desquamative	4	28.57%
	Ulcerative	8	61.54%	Ulcerative	2	14.28%

Note. * - difference is reliable (p<0.05).

The response degree of the bladder disorders in the patients of groups I and II was reliably different (p <0.05).

Thus, ulcerative reactions in group I were detected in 8 (61.54%) patients, while in the patients of group II there were 2 (14.28%), respectively, which is 4 times the value of the

results in group I and indicates a more pronounced damaging effect when the traditional EBRT and the Dimexidum solution are used.

Erosion-desquamative reactions in group I were found in 3 (23.07%) patients, and in group II in 4 (28.57%), which was not reliably different.

But, as far as catarrhal manifestations are concerned, the picture obviously favors group II of the study. In group I, 2 patients (15.38%) with catarrhal reaction were found, and in group II there were 8 (57.14%).

Analyzing the results obtained, it can be noted that the use of EBRT in the mode of the daily dose multi-fractionation reliably ($p = 0.05$) reduces the radiation reactions of the bladder mucosa.

Thus, the reactions of the 3-d degree (ulcerative) differ by 4.31 times in favor of group II (experimental) where the regimen of multi-fractionation and installations of the Emoxypine drug were used.

Reactions of the 2-nd degree (erosion-desquamative) differ by 1.24 times and also speak in favor of group II, but this indicator is unreliable.

Reactions of 1-st degree (catarrhal) differ by 3.72 times, which has a sufficient reliability in favor of treatment performed in group II of patients.

Summing up the comparison of the suggested regimens of the bladder radiation lesions treatment with the existing methods of this pathology therapy, one can conclude that up to now, no data have been published on the use of the Emoxypine drug which is aimed at regression of cystitis, treatment of the bladder ulcers. There is no practical literature data on the intracystic administration of this drug. The effect of the bladder installations in patients with radiation cystitis, complicated with an infectious process, in comparison with the traditional therapy methods permitted to shorten the patients' hospital stay by 6-7 days.

Thus, the performed study has shown that the used basic Dimexidum and Emoxypine drugs are targeted to different effects. Thus, with the pronounced fibrosis of the bladder wall and infectious process, the advantage can be given to the use of the Dimexidum solution, while in patients with hematuria and with destructions of the bladder wall integrity (erosion

or ulcerative-necrotic cystitis), the use of Emoxypine is the most effective. The choice of the treatment method should be based on subjective complains and on the objective study methods.

Conclusions. The results obtained with the use of the Emoxypine solution in comparison with the traditional treatment with Dimexidum testify to the prospects of the suggested method's further development, which reliably ($p = 0.05$) reduces the radiation responses.

1. Radiation lesions of the bladder are manifested in various forms of cystitis: uncomplicated (catarrhal, erosion-desquamative, atrophic and hemorrhagic); complicated (cystitis with profuse bleeding, ulcerous-necrotic).

2. Diagnostics of radiation cystitis should be comprehensive and based on the patients' complains (dysuria, hematuria, pain syndrome, etc.), on data of the laboratory and radiological diagnostic methods. Special attention should be paid to the ultrasound investigation and cystoscopy.

3. The efficacy of treatment in saline encrusted cystitis with severe pain syndrome is provided by the use of 5-10% Dimexidum solution, which efficacy made 56%. The pain syndrome was reversed in all patients.

4. The use of the Emoxypine drug with its anti-inflammatory, antioxidant, anti-aggregate effects permitted to improve the efficacy of treatment in patients with radiation cystitis: with ulcerative reactions – by 4.31 times, with erosion-desquamative reactions - by 1.24 times, with catarrhal ones – by 3.72 times, that is sufficiently reliable in favor of treatment performed in group II of the patients.

5. The choice of treatment for patients should be based on the nature and severity of the bladder wall radiation injuries. The therapy should be focused, first of all, on the infection fighting, on improving the immune status and on elimination of the bladder radiation fibrosis. The methods of choice are the Dimexidum and Emoxypine drugs used along with the symptomatic therapy.

Prospects for further research are continuation of the studies and search for the methods to prevent radiation reactions and complications during the radiotherapy, assessment of drugs and their combinations for the above pathologies.

Авторская декларация об оригинальности статьи и отсутствии плагиата

я (мы), Т.А. Zhukova, L.N. Vasko, V.F. Pocherniyayeva, N.A. Sokolova, O.V. Kornyejev

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