

THE ROLE OF IMMUNOTHERAPY IN THE PREVENTION OF THE SPECIAL TREATMENT COMPLICATIONS' DEVELOPMENT OF THE PATIENTS WITH THE ORAL CAVITY CANCER

*H. Hirna, M. Rozhko, I. Kostyshyn, V. Tkach, R. Levandovskyi, D. Maltsev*¹ Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine² Bukovinian State Medical University, Chernivtsi, Ukraine³ Bogomolets National Medical University, Kyiv, Ukraine

The article presents data concerning effectiveness of the immune agent alpha/beta defensins as a accompanying chemotherapy/radiotherapy drug at the 1st stage of treatment of 73 patients with cancer of the oral cavity and oropharynx.

The purpose of the work – to evaluate the effectiveness of the immune agent alpha/beta-defensins as a drug, accompanying radiation or chemoradiation therapy, at the 1st stage of treatment of patients with the oral cavity and oropharynx cancer.

Materials and methods. Patients of the I and II groups under study received radiation and chemoradiation therapy, respectively, as well as the immune agent alpha/beta defensins 2.0 ml 2 times a day intramuscularly 2 days before the start of the special treatment for 5 days, as well as during the next 10 days of treatment 1 time per day. Patients of III-IV groups, comparative, received similar treatment, but without immunotherapy.

The results. According to the time of the appearance of epitheliitis and changes in its degree in the dynamics of treatment, the best results were obtained in patients of group I, since the first inflammation manifestations in the oral cavity or oropharynx developed at the latest – at a dose of 22 Gy, while in patients of group III they appeared at a dose of 12 Gy ($p < 0.05$) and in larger quantity of patients (12%). The transition of the first degree of epitheliitis to II and III in the first group took place in a smaller number of patients, that indicates a positive effect of the immunopreparation on the severity of epitheliitis. The number of cases of epitheliitis of the III degree is indicative: 4% of patients of the I group against 79% of patients of the III group and 60% of patients of the IV on average after 30 Gy ($p < 0.05$). Only in the IV group there were patients who developed ulcerative epitheliitis (IV degree). The number of patients with radiodermatitis of the I degree in the I group was 30% less compared to the III group, in the II group – 29% less than in group IV. Radiodermatitis of the II degree was observed in a small number of patients – 5% in the II group and 11% in the III group Xerostomia occurred in 90% of patients regardless of the method of treatment and the use of immunotherapy as accompanying drug of special treatment. Paraesthesia and ageusia are more pronounced in groups III and IV.

Conclusions. The phenomena of radiation epitheliitis develop later in the treatment period and in a smaller number of patients, who received alpha/beta defensin immunotherapy compared to patients, who did not receive immunotherapy. A positive effect of immunotherapy can also be considered a decrease in the number of patients with III-IV degrees of epitheliitis.

Key words:

cancer of the oral cavity, oropharynx, telegamma therapy, chemotherapy, immunotherapy, radioepitheliitis, radiodermatitis, xerostomia.

Clinical and experimental pathology 2022. Vol.21, № 4 (82). P. 51-59.

DOI:10.24061/1727-4338.XXI.4.82.2022.08

E-mail: ggyma@ifnmu.edu.ua

РОЛЬ ІМУНОТЕРАПІЇ В ЗАПОБІГАННІ РОЗВИТКУ УСКЛАДНЕНЬ СПЕЦІАЛЬНОГО ЛІКУВАННЯ ХВОРИХ НА РАК РОТОВОЇ ПОРОЖНИНИ І РОТОГЛОТКИ*Г.А Гірна¹, М.М. Рожко¹, І.Д. Костишин¹, В.Є. Ткач¹, Р.А. Левандовський², Д.В. Мальцев³*¹ Івано-Франківський національний медичний університет, м. Івано-Франківськ, Україна² Буковинський державний медичний університет, м. Чернівці, Україна³ Національний медичний університет імені О.О. Богомольця, м. Київ, Україна

У статті наведені дані щодо ефективності імунного агента альфа/бета дефензинів, як препарату супроводу хіміо/променевої терапії на I-му етапі лікування 73 хворих на рак ротової порожнини і ротоглотки.

Мета роботи – оцінити ефективність імунного агента альфа/бета-дефензинів як лікарського засобу, що супроводжує променеву або хіміопротеневу терапію на I-му етапі лікування хворих на рак ротової порожнини та ротоглотки.

Матеріали та методи. Хворі I і II груп досліджуваних отримували променеву і хіміопротеневу терапію відповідно, а також імунний агент альфа/бета

Клінічна та експериментальна патологія. 2022. Т.21, № 4 (82)

Ключові слова:

рак порожнини рота, ротоглотка, телегамма-терапія, хіміотерапія, імунотерапія, радіоепітеліт, радіодерматит, ксеростомія.

Клінічна та експериментальна патологія 2022. Т.21, №4 (82). С. 51-59.

дефензинів по 2,0 мл 2 рази в день внутрішньом'язово за 2 дні до початку спеціального лікування протягом 5 днів, а також протягом наступних 10 днів лікування по 1 разу в день. Хворі III-IV груп, порівняльних, отримували аналогічне лікування, але без імунотерапії.

Результати. За термінами виникнення епітеліому і змінами його ступеня в динаміці лікування найкращі результати отримані у хворих I групи, оскільки перші прояви запалення в порожнині рота чи ротоглотки розвинулися найпізніше – на дозі 22 Гр, у той час як у пацієнтів III групи вони з'явилися на дозі 12 Гр ($p < 0,05$) та у більшій кількості пацієнтів (на 12%). Перехід I ступеня епітеліому в II і III в I групі мав місце у меншій кількості хворих, що свідчить про позитивний вплив імунпрепарату на тяжкість епітеліому. Показовою є кількість випадків епітеліому III ступеня: 4% пацієнтів I групи проти 79% хворих III групи і 60% хворих IV в середньому після 30 Гр ($p < 0,05$). Тільки у IV групі були хворі, в яких розвинувся виразковий епітеліом (IV ступеня). Кількість хворих із радіодерматитом I ступеня у I групі була на 30% меншою порівняно з III групою, у II групі – на 29% меншою, ніж у IV. У незначній кількості хворих спостерігали радіодерматит II ступеня – 5% у II групі та 11% – у III. Ксеростомія виникала у 90% пацієнтів незалежно від методу лікування та застосування імунотерапії як супровідного препарату спеціального лікування. Парагевзія і агевзія більш виражені в III і IV групах.

Висновки. Явища променевого епітеліому розвиваються в пізніші терміни лікування і в меншій кількості хворих, які отримували імунпрепарат альфа/бета дефензинів порівняно з пацієнтами, які не мали імунотерапії. Позитивним ефектом імунотерапії можна також вважати зменшення кількості хворих із III-IV ступенями епітеліому.

Introduction

Oral cavity cancer ranks the 17th place among the most common cancer types in the world [1]. Among all oncopathologies cancer of the mucous membrane of the oral cavity and oropharynx accounts for 1 to 3% in Ukraine. Every year more than 3000 new cases of cancer of the oral cavity and more than 1500 new cases of cancer of the oropharynx are registered in Ukraine [1]. In the Europe the 5-year survival rate is 50% [2], in the USA – 65% [3], in East Asia, Africa, Central America – 35-54% [4]. In Ukraine, the 5-year survival of the stage I is 75-80%, stage II – is 50-60% and stage III – 30-40% [5]. The presence of complications of special treatment methods affects the quality of treatment and, accordingly, the survival rate of patients with oral cavity cancer [6].

Most often, 80% of patients have such a complication as oral mucositis, which affects the quality and safety of life of the patient, the possibility of completing the planned phase of treatment [7]. With the development of oral mucositis, as a consequence, the following complications occur: violation of the formation of food bolus in 92.8%, and then nutrition; general weakness in 62%; headache in 35% of patients; conversation disturbance in 29%; sleep disorders in 25%; depression in 38% of patients. In 93% of cases there is a xerostomia, dysgeusia in 56%. Radiodermatitis develops in 95% of patients [7].

The aim of research

To evaluate the effectiveness of the immune agent alpha/beta-defensins as a drug, accompanying radiation or chemoradiation therapy, at the 1st stage of treatment of patients with the oral cavity and oropharynx cancer

Materials and methods

The study included patients with cancer of the oral cavity and oropharynx of all stages, who were divided into groups depending on the method of treatment at the 1st stage of

treatment. Patients of groups I and II received radiation and chemoradiation therapy, respectively, as well as the immune preparation alpha/beta-defensins. Patients in groups III-IV, respectively, received similar treatment, but without immunotherapy. All patients signed an informational agreement on the treatment plan, following the principles of the Helsinki Declaration and the decision of the Ethics Commission of Ivano-Frankivsk National Medical University (study protocol – № 94/17 of 16.11.2017).

Immune complex of alpha/beta-defensins increases the number of T-lymphocytes, enhances the cytotoxic effect of macrophages against tumor cells. It has anti-metastatic and antitumor effects, reduces the severity of side effects of chemoradiation treatment [8]. In this study, the scheme of its use is as follows: 2.0 ml 2 times a day intramuscularly 2 days before the start of specialized treatment for 5 days and once a day during the next 10 days of treatment [9, 10].

Among 73 patients, there were 9 (12%) women and 64 (88%) men. The youngest patient was 33 years old, the oldest was 82 years old, the average age was – $59.7 \pm 1,08$ years.

In group I (RT + IT) there were 25 patients, group II (RT + IACT + IT) and group III (RT) – 19 patients each, and in group IV (RT + IACT) – 10 patients.

In group I (RT + IT) 12 (48%) patients with oropharyngeal cancer, 1 (4%) of them had a tumor of the proper root of the tongue and 6 (24%) patients – of the soft palate, in other 5 (20%) patients due to the prevalence of the tumorigenic process it was difficult to indicate the initial location of the oropharyngeal tumor. There were 3 (12%) patients who had a tumor of the lateral part of the bottom of the oral cavity, 4 (16%) patients – of the frontal part of the bottom of the mouth. In 2 (8%) patients there was cancer of the mucous membrane of the cellular part of the lower jaw and in 1 (4%) patient – of the upper jaw. There was 1 (4%) patient having a tumor of the hard palate, retromolar area and the moving part of the tongue.

The distribution of patients depending on the stage of the disease was as follows: 1 (4%) – patient with stage I, 5 (20%) – with stage II, 8 (32%) – with stage III, 11 (44%) – with stage IV.

There were: 1 (4%) patient with exophytic tumor, 16 (64%) patients with endophytic tumor and 8 (32%) with mixed tumor growth.

8 (32%) patients had squamous cell carcinoma with a degree of differentiation of G1, 10 (40%) – with G2, and 7 (28%) with G3.

Patients of group I at the first stage of special treatment received a course of gamma teletherapy of SFD at 2 Gy against a background of immune agent alpha/beta-defensins. The dose of radiation therapy in 18 (72%) patients was 40 Gy, in 1 (4%) patient – 44 Gy, 4 (16%) patients received 38 Gy, and 1 (4%) patient – 34 Gy, and another 1 (4%) – 26 Gy.

There were 19 patients in group II (RT + IACT + IT). There were 6 (32%) patients with oropharyngeal cancer, 4 of them had cancer of the tongue root, 2 patients developed cancer of the tonsil. 8 (42%) patients had a tumor of the tongue, 4 (21%) patients – the lateral part of the bottom of the oral cavity, and 1 (5%) – the frontal part of the bottom of the mouth. Only in 1 (5%) patient the tumor did not spread to neighboring areas.

There were no patients with stage I in group II. Stage II was diagnosed in 1 (5%) patient, stage III in 12 (63%) patients and stage IVA – in 6 (32%) patients.

The form of tumor growth in 1 (5%) patient was exophytic, in 14 (74%) – it was endophytic and in 4 (21%) – it was the mixed form of tumor growth. 5 (26%) patients had squamous cell carcinoma with a degree of differentiation of G1, 11 (58%) – G2, and 3 (16%) with G3.

Chemoradiation treatment was performed in patients of group II. 14 (74%) patients received 40 Gy at the first stage of radiation therapy, 3 (16%) patients – 38 Gy, and 1 (5%) patient 36 Gy and 20 Gy, respectively. Chemotherapeutic potentiation was performed with cisplatin RD 20 mg/m² during 5 days from the date of initiation of radiation therapy [8]. Chemotherapy was administered through the superficial temporal artery to 15 (78%) patients, 2 (11%) patients were performed bilateral catheterization through the same artery and 2 (11%) – through the external carotid artery. The minimum dose of introduced cytostatic was 100 mg, the maximum – 200 mg. The average dose, administered to patients, was 125 mg.

Among 19 patients of group III (RT) there were 7 (37%) with oropharyngeal cancer, 1 had a tumor of the soft palate and 1 – of the root of the tongue, in 5 other patients the primary area of tumor formation cannot be specified. There were 4 (21%) patients who were diagnosed with cancer of the lateral part of the bottom of the oral cavity, and frontal – in 3 (16%) patients. There were 3 (16%) patients with cancer of the tongue, 1 (5%) patient with cancer of the retromolar area, also 1 (5%) patient with cancer of mucosal cell of the mandible, 14 (74%) patients had tumor spread to neighboring areas.

Among patients of this group, 9 (47%) patients were with stages III and 10 (53%) patients with stage IV.

There were 3 (16%) patients with exophytic tumor, 10 (53%) with endophytic and 6 (31%) with mesophytic, 5 (26%) patients had squamous cell carcinoma with

a degree of differentiation G1, 12 (63%) – with G2, and 2 (11%) with G3.

Patients of the comparative group III received similar treatment as patients in group I, but immunotherapy was not included in the scheme of concomitant therapy. According to the 1st stage of special treatment, 11 (58%) patients received 40 Gy of radiation therapy, 3 (16%) patients – 38 Gy, also 3 (16%) patients – 36 Gy, and 1 (5%) patient – 22 and 20 Gy, respectively.

Group IV consisted of 10 patients: 4 (40%) patients had cancer of the oropharynx, 3 (30%) patients had cancer of the tongue, and 1 (10%) patient had cancer of the palate, 1 (10%) patient had cancer of mucous membranes of the frontal part of the oral cavity and 1 (10%) patient had cancer of the cheek.

The staging of patients in this group was as follows: 5 (50%) patients with stage III, 4 (40%) patients – with stage IVA and 1 (10%) patient with stage IVB. There were 6 (60%) patients with endophytic form of tumor growth and 4 (40%) with mixed form. According to the degree of differentiation, 3 (30%) patients had squamous cell carcinoma G1, 6 (60%) patients – G2 and 1 (10%) patient – G3.

There were 5 (50%) patients who received 40 Gy at the first stage of radiation therapy, 2 (20%) – 38 Gy, 2 (20%) – 36 Gy, 1 (10%) – 34 Gy, 2 (20%) of them received special palliative treatment. All patients were performed chemotherapeutic potentiation with cisplatin through the superficial temporal artery, and in 1 (10%) patient bilateral catheterization of this artery was performed. The average total dose of cisplatin was 129.5 mg. The minimum total dose, received by the patient, was 80 mg and the maximum was 200 mg.

Statistical processing and analysis of the results were performed according to the generally accepted methods using licensed statistical analysis programs Statistica v.6.1 (StatSoft Inc., serial № AGAR909E415822FA) and Microsoft Excel. The probability of statistical studies was assessed using Student's t-test.

Results and discussion

Complications of patients with cancer of the oral cavity and oropharynx, who received radiation and chemoradiation therapy at the 1st stage of special treatment, were evaluated. All patients received concomitant therapy topically using radioprotectors, antiseptics and keratoplasty medicines. Dynamic monitoring was performed for the presence of oral mucositis in the oral cavity or oropharynx, radiation dermatitis, their degree, timing and duration.

Observing patients of group I, it is possible to note that in 2 (8%) patients there were no complaints of dryness in a mouth, accordingly in 23 patients they developed on the average after the dose of 18.78±1.63 Gy. Complaints of saliva viscosity occurred on average beginning with the dose of 21.30±1.47 Gy in 20 (80%) patients.

Another complication of radiation therapy – hypogeusia (reduction of taste sensations) occurred in 23 (92%) patients, on average after the dose of 17.65±1.30 Gy, in 2 (8%) patients there were no complaints of decreased taste sensations. Parageusia (distortion of taste sensations) was in 2 (8%) patients after the dose of 27.00±1.0 Gr. Ageusia – complete loss of taste, was in 11

(44%) patients with an average dose of 32.73 ± 0.91 Gr, respectively, 14 (56%) patients did not have ageusia.

Analysis of the most common complication in patients with cancer of the oral cavity or oropharynx, namely oral mucositis, is represented by the following data: in 3 (12%) patients of group I oral mucositis phenomena during treatment were not observed. In 22 (88%) patients the oral mucositis of the I degree (catarrhal) has developed, on average after the dose of 23.55 ± 1.27 Gy, in 12 (48%) of whom, the degree of oral mucositis deepened to II (focal) on average after the dose of 26.17 ± 1.87 Gy. Only in 1 (4%) patient the II degree passed into the III degree (membranous) after the dose of 30 Gy.

Mandatory intermediate control over the development of oral mucositis was half of the planned treatment; this was the period, when patients in the groups under study (I and II), completed immunotherapy, on average it was 20 Gy. At that time, the dynamics of complications and their degree were assessed. In 18 (72%) patients oral mucositis has not developed yet, in 3 (12%) patients there was oral mucositis of the I degree (catarrhal), and in 4 (16%) patients – the II degree (focal).

In general, after the completion of the 1st stage of radiation treatment in 3 (12%) patients there was no oral mucositis, 11 (44%) patients had only I degree (catarrhal) oral mucositis, 10 (40%) – II (focal) degree and in 1 (4%) – III (membranous).

Assessment of radiation dermatitis showed that radiodermatitis of the I degree developed only in 3 (12%) patients on average after the dose of 28.67 ± 5.46 Gy. And accordingly, in 22 (88%) patients it was not observed.

Against a background of the developed complications in some patients there were the following complaints: loss of appetite in 2 (8%) patients, swallowing disorders in 3 (12%) patients and eating disorders in 4 (16%) patients. Radiation laryngitis, which was manifested by hoarseness and inflammation, laryngoscopically was in 5 (20%) patients with the dose of 26 Gy.

In patients of group II, dry mouth on average has also began after the dose of 18.82 ± 1.66 Gy, only 2 (11%) patients did not have it. Saliva viscosity bothered 15 (79%) patients, on average after the dose of 21.60 ± 1.89 Gy.

Decreased taste sensitivity was in 17 (89%) patients and on average after 17.25 ± 1.90 Gy, and in 2 (11%) patients it was not observed. Distortion of taste properties was in 2 (11%) patients. On average, after the dose of 28.75 ± 1.81 Gy, 8 (42%) patients had ageusia, respectively, 11 (58%) patients did not have it.

During the treatment, on average after the dose of 20.43 Gy the 1st (catarrhal) degree of oral mucositis has developed in 14 (74%) patients. Subsequently, after 24.89 ± 1.60 Gy the phenomena of inflammation of the mucous membrane of the oral cavity and oropharynx were deepened up to the II (focal) degree in 9 (47%) patients. And the membranous form of the II degree of oral mucositis – in 3 (16%) patients after the dose of 22.67 ± 1.76 Gy. 2 (11%) patients had III (membranous) degree of oral mucositis which developed from the II degree after the dose of 22.00 ± 2.00 Gy.

After completion of immunotherapy, at a dose of 20 Gy of radiation therapy, in 8 (42%) patients oral mucositis has not yet developed, 7 (37%) patients

had oral mucositis of the I (catarrhal) degree, 3 (16%) patients – II (focal) degree and in 1 (5%) patient – the II degree but a membranous form.

Thus, in this group at the end of treatment in 5 (26%) patients the oral mucositis phenomena were not observed, 2 (11%) patients had I (catarrhal) degree, 8 (42%) – II (focal) and 1 (5%) – II (membranous), as well as 3 (16%) patients had III (membranous) degree of oral mucositis.

There was no radiodermatitis in 13 (68%) patients. 6 (32%) patients after the dose of 23.33 ± 4.40 Gr had dermatitis of the I degree and in 1 (5%) of them it passed into the II degree after the dose of 38 Gy and in one – into the III degree at the dose of 14 Gy.

Among other complications, it should be noted that 2 (11%) patients had loss of appetite, the other 2 (11%) – swallowing disorders, and eating disorders in 4 (21%) patients. Speech disorders due to complications were in 1 (5%) patient. Radiation laryngitis was present in 7 (37%) patients at a dose of 28.86 ± 2.57 Gy. Trismus in 1 (5%) patient and candidiasis – in 1 (5%) patient occurred after chemotherapy.

Patients of group II were performed chemotherapeutic potentiation with cisplatin according to the scheme. In some cases, during the administration of medicine, there was toxic paresis of the facial nerve, paresthesia, increased blood pressure, tearing and in 2 (11%) patients – nausea and vomiting.

Xerostomia in group III was in 17 (89%) patients and on average it began with the dose of 12.44 ± 1.15 Gy. Also in these patients, complaints of increased salivary viscosity arose on average from the dose of 18.47 ± 1.68 Gy.

Regarding the violation of taste properties, the following was observed: hypogeusia in 17 (89%) patients on average after 11.41 ± 0.82 Gy, parageusia in 1 (5%) patient, and ageusia in 12 (63%) patients with an average dose of 29.67 ± 0.95 Gy, respectively 7 (37%) patients did not have ageusia.

All patients in this group developed catarrhal oral mucositis on average after a dose of 12.21 ± 0.75 Gy, in 18 (95%) patients radial inflammation of the oral mucosa deepened up to II (focal) degree on average after 21.11 ± 1.27 Gy and in 1 (5%) patient the focal form of oral mucositis has transformed into the membranous one of the II degree. In 15 (79%) patients, oral mucositis of the II (focal) degree passed into the III (membranous) on average after the dose of 30.93 ± 1.07 Gy.

After immunotherapy, 10 (53%) patients in this period of treatment had oral mucositis of the I (catarrhal) degree, 8 (42%) patients – II (focal) degree and 1 (5%) – II degree, but membranous form.

Summarizing the observation of patients of group III at the end of treatment, 1 (5%) patient had oral mucositis of the I (catarrhal) degree, 3 (16%) – II (focal) degree, and 15 (79%) patients – III (membranous) one.

In this group there were more patients with radiation dermatitis of the I degree than in the previous two, namely – 11 (58%) patients, on average after the dose of 28.36 ± 1.57 Gy. In 2 (16%) of them after 34 Gy the dermatitis of the II degree, and in 1 (5%) – of the III and later of the IV degree has developed, 8 (42%) patients did not notice the appearance of complications on the skin of the neck and face.

Comparing patients of groups I and III according to the type of treatment, there was also a greater number of patients who complained of loss of appetite, more precisely – 8 (89%) after 25.00 ± 3.38 Gy, eating disorders – in 8 (42%) patients after the dose of 27.75 ± 2.52 Gy, and swallowing disorders – in 6 (32%) patients after the dose of 31.33 ± 1.23 Gy. Radiation inflammation of the larynx was in 4 (21%) patients on average after the dose of 32.50 ± 1.71 Gy. Candidiasis was also observed in 1 (5%) patient at a dose of 12 Gy.

Complaints of dry mouth began on average after 9.78 ± 1.18 Gy in 9 (90%) patients, and saliva viscosity in 7 (70%) patients on average after 11.71 ± 2.11 Gy 1 (10%) patient had increased salivation due to the swallowing difficulty.

Hypogeusia occurred in 9 (90%) patients and on average after 12.67 ± 2.54 Gy, in 1 (10%) patients there were no complaints of decreased taste sensations. Parageusia was in 3 (30%) patients, after 21.33 ± 3.33 Gy, ageusia in 6 (60%) patients with an average dose of 29.33 ± 2.72 Gy.

In 10 (100%) patients the catarrhal oral mucositis has developed, on average after the dose of 13.00 ± 1.44 Gy, in 8 (80%) of them the degree of oral mucositis deepened to II (focal) on average after 19.75 ± 1.53 Gy, and later in the II degree (membranous) in 5 (50%) patients after 23.50 ± 2.36 Gy. In 6 (60%) patients the II degree has transferred into the III (membranous) after the dose of 30.00 ± 1.37 Gy.

Half of the performed stage of treatment of group IV patients was characterized by the presence of I (catarrhal) degree of oral mucositis in 3 (30%) patients, in 5 (50%) patients – II degree (focal) and in 1 (10%) patient the II degree, membranous form, 1 (10%) patient had no oral mucositis.

At the end of the treatment, 1 (10%) patient had catarrhal oral mucositis, 1 (10%) patient had the II degree of oral mucositis, focal form, 2 (20%) patients had the II degree of oral mucositis, membranous form and 5 (50%) – III (membranous). Only in this group after

the treatment the IV (ulcerative-necrotic) degree has developed in 1 (10%) patients.

The phenomena of radiation dermatitis were not observed in 4 (40%) patients. 6 (60%) patients had the I degree of dermatitis after 22.80 ± 4.59 Gy. In 1 (10%) of them it has quickly transferred from the I to the IV degree.

The presence of complications contributed to eating disorders in 4 (40%) patients after the dose of 22.40 ± 4.53 Gy, swallowing disorders in 4 (40%) patients after the dose of 22.80 ± 2.06 Gy. Loss of appetite was in 3 (30%) patients after the dose of 15.00 ± 3.87 Gy. Radiation laryngitis was present in 2 (20%) patients with 32.00 ± 4.0 Gy. Trismus in 1 (10%) patient, which is more associated with chemotherapy performed, and candidiasis in 1 (10%) patient after the dose of 20 Gy, were observed.

Chemotherapeutic potentiation with cisplatin in addition to the increase of the duration of the development and the degree of oral mucositis also caused toxic paresis of the facial nerve in 1 (10%) patient and otitis in another.

According to the data given above, we can say that 90% of all patients had xerostomia of the I degree (Fig. 1). Only 2 patients in groups I and II did not have this complication. The difference between the groups is in the timing of dry mouth and then the viscosity of saliva. In the research groups they were the same, on average after the dose of 18 Gy and in groups III and IV xerostomia occurred at a dose of 8 Gy and 10 Gy, respectively. Comparing groups I and III, xerostomia was observed at a dose of 8 Gy earlier in the group under study than in the comparison group. Indicators between groups II and III were significant ($p < 0.05$). Xerostomia in group IV appeared 10 Gy quicker, comparing it with group II. Complaints about the viscosity of saliva in groups I, II and III were received almost at the same time, on average after the dose of 18–20 Gy, only in group IV they arose quicker, after the dose of 10 Gy, which can be explained by chemotherapeutic potentiation of cisplatin and not immunotherapy use as a maintenance medicine. Between groups I and IV the indicators were significant ($p < 0,01$).

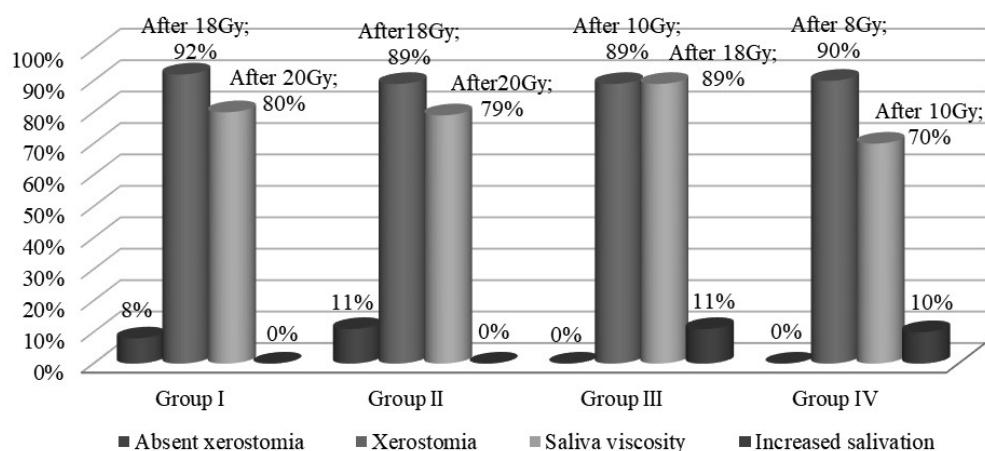


Fig. 1. Indicators of salivation disorders and their timing in groups of patients with cancer of the oral cavity and oropharynx.

The most common manifestation of taste change was hypogeusia in all groups, on average in 90% of patients. In terms of occurrence, in the control groups it was quicker.

Comparing the groups according to the type of special treatment, namely groups I and III, in the comparison group – III, hypogeusia occurred 6 Gy quicker, and in

group IV – 4 Gy faster than in group II. As can be seen from Fig. 2, the development of parageusia was less than ageusia. Thus, in group I and II it was only in 8% of patients and 11%, respectively, also in group III – in 5% of patients. More often this complication was in the comparison group – IV, which received chemotherapeutic potentiation. There were 30% of patients, compared to the previous groups – it is a high figure and somewhat quicker timing – at the dose of 22 Gy.

The largest number of complete loss of taste sensations was in group III – it is in 63% of patients, almost as many as in group IV; it was manifested on average after the dose of 28 Gy in both groups. At the same time, ageusia was manifested in the research group II in a smaller number of patients – 42%. The least amount of patients with this complication was in group I – 11%, after the dose of 32 Gy. Reliable data are indicators of ageusia between groups I and III ($p < 0,05$).

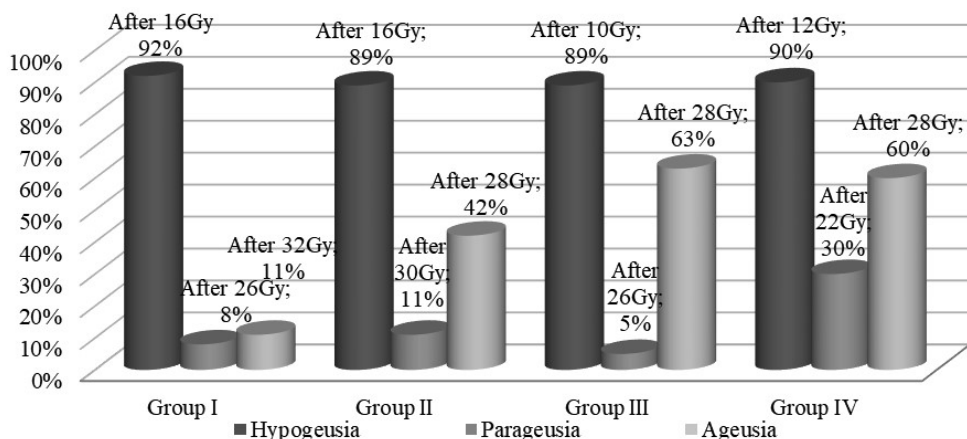


Fig. 2. Indicators of taste disorders in patients with cancer of the oral cavity and oropharynx and the timing of their occurrence.

Observations of the timing of oral mucositis and changes in its degree in the dynamics of treatment are shown in Fig. 3. As can be seen, the best results are in group I of patients, because the first manifestations of inflammation in the oral cavity or oropharynx developed later, at a dose of 22 Gy. In comparison with group III, it was later, at the dose of 10 Gy. As to the number of patients, this is 12% less than in group III. The transition of the I degree into the II and III

in the group I is fast, but in a smaller number of patients, that indicates a positive effect of the immune drug on the degree of oral mucositis. Indicative are the results of the presence of oral mucositis of the III degree in 4% of group I against 79% of patients of group III and 60% of patients of group IV on average after the dose of 30 Gy. In fact, most often oral mucositis of the III degree developed after the dose of 30 Gy in all groups except group II.

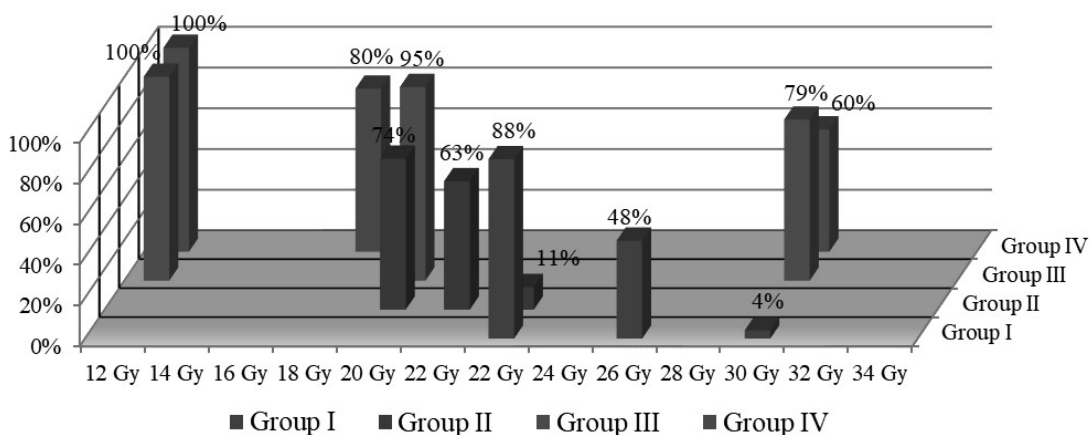


Fig. 3. Dynamics of transition of oral mucositis of the I degree into the III one in groups of patients with cancer of the oral cavity and oropharynx.

The dynamics of oral mucositis development in groups II and IV is the following: I degree arose 8 Gy later in 74% of patients of group II than in patients of group IV ($p < 0,05$). At the dose of 20 Gy, patients of group II have only developed oral mucositis of the I degree, and most patients of groups III and IV developed oral mucositis of the II degree. By the end of treatment in patients of group IV, the II degree of oral mucositis has changed to the III one in 60%, which is 49% more ($p < 0,05$) than in group II.

The full development of oral mucositis by the end of treatment in groups can be seen in Fig. 4. Thus, in 12% of patients of group I and 26% of group II oral mucositis phenomena were not observed by the end of treatment, 44% and 40% of patients had catarrhal and focal oral mucositis in group I. In group II there were more patients with focal oral mucositis – 42%. Most patients were in group III with membranous oral mucositis – 79%, which is 75% more than in group I ($p < 0,05$). In group IV, most

patients also had membranous oral mucositis – 50%, and in comparison with group II, it is 34% more ($p<0,05$), that is associated with the transition of the II degree to the III degree, which was not observed in group II. Only in group IV there were patients who developed the ulcerative oral mucositis of the IV degree.

The membranous form of oral mucositis of the II degree, and these are membranous erosions up to 1.5 cm were only in groups II and IV, in which chemotherapeutic potentiation was performed. Accordingly, it was 5% against 20% ($p<0,05$). 15% more patients were in group IV, where no immunotherapy was performed.

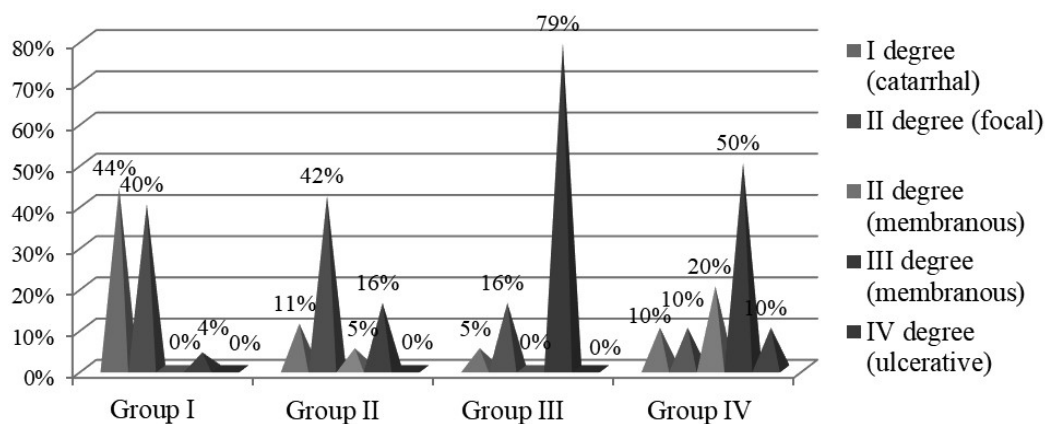


Fig. 4. Indicators of oral mucositis according to the degree and form in groups of patients with cancer of the oral cavity and oropharynx.

Radiodermatitis occurred to less extent than oral mucositis. Thus, radiodermatitis of the I degree was most often observed, more often in group IV – in 50% of patients, slightly less in group III – 42%. Comparing these data with the observation groups, we can say that in group I, the I degree of dermatitis was 30% less

than in group III ($p<0,05$). In group II dermatitis of the I degree arose at 29% of patients less than in group IV ($p<0,05$). A small number of patients had the II degree of radiodermatitis, only 5% in group II and 11% in group III. In group IV, it has quickly transferred into the IV degree in 10% (Fig. 5).

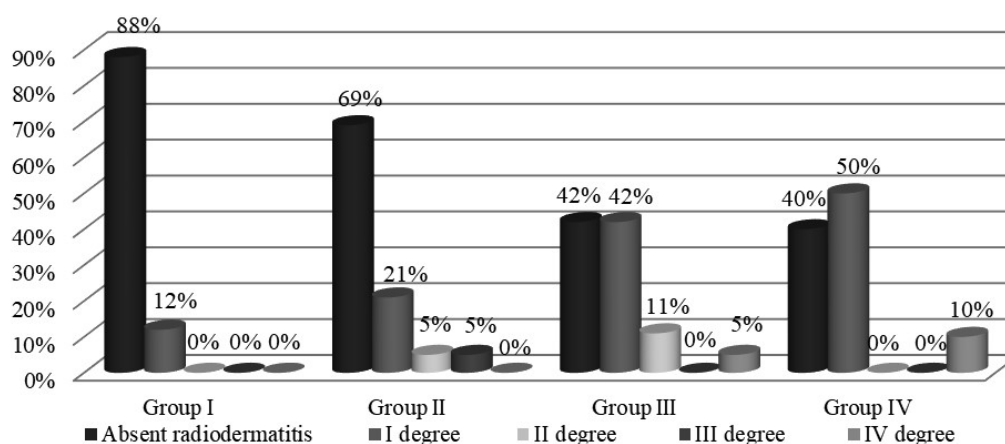


Fig. 5. Indicators of radiodermatitis according to the degree in groups of patients with cancer of the oral cavity and oropharynx.

Due to the individual tolerability of complications in patients, additional systemic anti-inflammatory therapy, antibiotic therapy or dehydrating therapy were performed. Thus, in groups I and II there were 5 such patients. In group III – 1 patient and in group IV – 3 patients. To reduce the effects of complications that influenced the safety of radiation or chemoradiation therapy in a certain period of treatment was suspended: 1 patient in group I, 3 patients in group II, 2 patients in group III and 1 patient in group IV.

Conclusions

1. Immune agent alpha/beta-defensins has a positive influence on the reduction of the number of complications of special treatment of patients with cancer of the oral cavity and oropharynx. Thus, oral mucositis occurred at a later

date and in fewer patients who received chemotherapy/radiation therapy with immunotherapy. Severe III degree of oral mucositis was present in a small number of patients.

2. In patients who did not receive immunotherapy of alpha/beta-defensins, oral mucositis developed rapidly, and in a large number of patients the degree of inflammatory lesion deepened.

3. Xerostomia occurred in 90% of patients regardless of the method of treatment and use of immunotherapy as a maintenance medicine. Xerostomia, as well as saliva viscosity occurred faster in the group of patients receiving chemoradiation treatment without immunotherapy (group IV).

4. Violation of taste properties was in 90% of patients with cancer of the oral cavity and oropharynx of

all groups. Parageusia and ageusia are more pronounced in groups III and IV.

5. In patients of groups of comparison (without immunotherapy of alpha/beta-defensins) inflammatory changes of skin were met more often than in the research groups, and for the most part it was oral mucositis of the I degree.

6. The appointment of the immune agent alpha/beta-defensins in the treatment of cancer of the oral cavity and oropharynx is reasonable and appropriate, which facilitates the easier course of complications and the completion of the planned treatment.

Conflict of interest

The authors report no conflict of interest.

Список літератури

- Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30. doi: 10.3322/caac.21590
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-49. doi: 10.3322/caac.21660
- Eloranta S, Smedby KE, Dickman PW, Andersson TM. Cancer survival statistics for patients and healthcare professionals – a tutorial of real-world data analysis. *J J Intern Med.* 2021;289(1):12-28. doi: 10.1111/joim.13139
- Andersson TML, Rutherford MJ, Myklebust TÅ, Møller B, Soerjomataram I, Arnold M, et al. Exploring the impact of cancer registry completeness on international cancer survival differences: a simulation study. *Br J Cancer.* 2021;124(5):1026-32. doi: 10.1038/s41416-020-01196-7
- Федоренко ЗП, редактор. Рак в Україні, 2020-2021. Захворюваність, смертність, показники діяльності онкологічної служби. Бюлетень Національного канцер-реєстру № 23 [Інтернет]. Київ; 2022[цитовано 2023 Січ 23]. Доступно: http://www.ncru.inf.ua/publications/BULL_23/index.htm
- Tervo S, Seppälä M, Rautiainen M. The expression and prognostic relevance of programmed cell death protein 1 in tongue squamous cell carcinoma. *APMIS.* 2020;128(12):626-36. doi: 10.1111/apm.13084
- Sroussi HY, Epstein JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. *Cancer Med.* 2017;6(12):2918-31. doi: 10.1002/cam4.1221
- Hirna HA, Maltsev DV, Natrus LV, Rozhko MM, Kostyshyn ID, Tanasychuk IS. Study of the immunomodulating influence of preparation alpha/beta-defensins on chemo/radiotherapy of patients with oral and oropharyngeal cancer. *Фізіологічний журнал.* 2021;67(4):86-96. doi: 10.15407/fz67.04.086
- Гірна ГА, Костишин ІД, Рожко ММ, Лукач ЕВ, Андрієв АВ. Значення імунотерапії препаратом альфа-бета-дефензинів у розвитку епітеліту у хворих на орофарингеальний рак. *Клінічна онкологія.* 2021;11(3-4):36-37. doi: 10.32471/clinicaloncology.2663-466X.43-3.28502
- Цюпа І. Лімфома в Україні: стан проблеми сьогодні та перспективи її вирішення у майбутньому. *Здоров'я України. Онкологія, Гематологія, Хіміотерапія.* 2020;4:8-10.
- Siegel RL, Miller KD, Jemal A. *Cancer Statistics, 2020.* *CA Cancer J Clin.* 2020;70(1):7-30. doi: 10.3322/caac.21590
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* *CA Cancer J Clin.* 2021;71(3):209-49. doi: 10.3322/caac.21660
- Eloranta S, Smedby KE, Dickman PW, Andersson TM. *Cancer survival statistics for patients and healthcare professionals – a tutorial of real-world data analysis.* *J J Intern Med.* 2021;289(1):12-28. doi: 10.1111/joim.13139
- Andersson TML, Rutherford MJ, Myklebust TÅ, Møller B, Soerjomataram I, Arnold M, et al. *Exploring the impact of cancer registry completeness on international cancer survival differences: a simulation study.* *Br J Cancer.* 2021;124(5):1026-32. doi: 10.1038/s41416-020-01196-7
- Fedorenko ZP, редактор. *Рак в Україні, 2020-2021. Zakhvoriuvanist', smertnist', pokaznyky diial'nosti onkologichnoi sluzhby [Cancer in Ukraine, 2020-2021. Morbidity, mortality, performance indicators of the oncology service].* *Biuletent' Natsional'noho kantser-reiestru № 23 [Internet].* Kyiv; 2022[tsytovano 2023 Sich 23]. Dostupno: http://www.ncru.inf.ua/publications/BULL_23/index.htm (in Ukrainian)
- Tervo S, Seppälä M, Rautiainen M. *The expression and prognostic relevance of programmed cell death protein 1 in tongue squamous cell carcinoma.* *APMIS.* 2020;128(12):626-36. doi: 10.1111/apm.13084
- Sroussi HY, Epstein JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, et al. *Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis.* *Cancer Med.* 2017;6(12):2918-31. doi: 10.1002/cam4.1221
- Hirna HA, Maltsev DV, Natrus LV, Rozhko MM, Kostyshyn ID, Tanasychuk IS. *Study of the immunomodulating influence of preparation alpha/beta-defensins on chemo/radiotherapy of patients with oral and oropharyngeal cancer.* *Fiziologichnyi zhurnal.* 2021;67(4):86-96. doi: 10.15407/fz67.04.086
- Hirna HA, Kostyshyn ID, Rozhko MM, Lukach YeV, Andriiv AV. *Znachennia imunoterapii preparatom al'fa/beta-defenzyniv u rozvytku epiteliitu u khvorykh na orofaryngeal'nyi rak [The value of the immunotherapy of alfa/beta defensins in the development of epitheliitis in patients with oropharyngeal cancer].* *Klinichna onkologhiia.* 2021;11(3-4):36-37. doi: 10.32471/clinicaloncology.2663-466X.43-3.28502 (in Ukrainian)
- Tsiupa I. *Limfoma v Ukraini: stan problemy s' ohodni ta perspektyvy yii vyrishennia u maibutn'omu [Lymphoma in Ukraine: the state of the problem today and prospects for its solution in the future].* *Zdorov'ia Ukrainy. Onkologhiia, Hematologhiia, Khimioterapiia.* 2020;4:8-10. (in Ukrainian)

References

Information about the authors:

Hirna H. – assistant of the Department of Oncology and the Department of Dentistry, Educational and Scientific Institute of Postgraduate Education of the Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine.

E-mail: halynagirna@gmail.com

ORCID ID: <https://orcid.org/0000-0003-1492-5349>

ISSN 1727-4338 <https://www.bsmu.edu.ua>

Клінічна та експериментальна патологія. 2022. Т.21, № 4 (82)

Rozhko M. – Doctor of Medicine, Professor, Corresponding member of the National Academy of Medical Sciences of Ukraine, Professor of the Department of Dentistry of the Educational and Scientific Institute of Postgraduate Education of the Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine.

E-mail: stomatfpo@ifnmu.edu.ua

ORCID ID: <https://orcid.org/0000-0002-6876-2533>

Kostyshyn I. – Ph.D. in Medicine, Associate Professor of the Department of Oncology, Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine.

E-mail: ivankostyshyn30@gmail.com

ORCID ID: <https://orcid.org/0000-0002-2893-5153>

Tkach V. – Honored doctor of Ukraine, Ph.D. in Medicine, Associate Professor of the Department of Dermatology and Venereology, Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine, Ivano-Frankivsk, Ukraine.

E-mail: dermatology@ifnmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5560-392>

Levandovskiy R. – Doctor of Medicine, Associate Professor of the Department of Orthopedic Dentistry, Bukovinian State Medical University, Chernivtsi, Ukraine.

E-mail: r.lev@ukr.net

ORCID ID: <https://orcid.org/0000-0002-5571-6095>

Maltsev D. – Ph.D. in Medicine, Associate Professor, Head of the Laboratory of Immunology and Molecular Biology, Institute of Experimental and Clinical Medicine, O. O. Bogomolets National Medical University, Kyiv, Ukraine.

E-mail: dmaltsev@ukr.net

ORCID ID: <https://orcid.org/0000-0002-6615-3072>

Відомості про авторів:

Гірна Г. А. – асистент кафедри онкології та кафедри стоматології навчально-наукового інституту післядипломної освіти Івано-Франківського національного медичного університету Міністерства охорони здоров'я України, м. Івано-Франківськ, Україна.

E-mail: halynagirna@gmail.com

ORCID ID: <https://orcid.org/0000-0003-1492-5349>

Рожко М. М. – д.мед.н., професор, член-кореспондент Національної академії медичних наук України, професор кафедри стоматології навчально-наукового інституту післядипломної освіти Івано-Франківського національного медичного університету Міністерства охорони здоров'я України, м. Івано-Франківськ, Україна.

E-mail: stomatfpo@ifnmu.edu.ua

ORCID ID: <https://orcid.org/0000-0002-6876-2533>

Костишин І. Д. – к.мед.н., доцент кафедри онкології Івано-Франківського національного медичного університету Міністерства охорони здоров'я України, м. Івано-Франківськ, Україна.

E-mail: ivankostyshyn30@gmail.com

ORCID ID: <https://orcid.org/0000-0002-2893-5153>

Ткач В. Є. – к.мед.н., доцент кафедри дерматології та венерології Івано-Франківського національного медичного університету Міністерства охорони здоров'я України, м. Івано-Франківськ, Україна.

E-mail: dermatology@ifnmu.edu.ua

ORCID ID: <https://orcid.org/0000-0001-5560-392>

Левандовський Р. А. – д.мед.н., доцент кафедри ортопедичної стоматології Буковинського державного медичного університету, м. Чернівці, Україна.

E-mail: r.lev@ukr.net

ORCID ID: <https://orcid.org/0000-0002-5571-6095>

Мальцев Д. В. – к.мед.н., доцент, завідувач лабораторії імунології та молекулярної біології Інституту експериментальної і клінічної медицини Національного медичного університету імені О. О. Богомольця, м. Київ, Україна.

E-mail: dmaltsev@ukr.net

ORCID ID: <https://orcid.org/0000-0002-6615-3072>

Стаття надійшла до редакції 05.12.2022

© Г.А. Гірна, М.М. Рожко, І.Д. Костишин, В.Є. Ткач, Р.А. Левандовський, Д.В. Мальцев

