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UTICAJ RADIOTERAPIJE I HEMOTERAPIJE NA ORALNA TKIVA

THE EFFECTS OF RADIOTHERAPY AND CHEMOTHERAPY ON ORAL TISSUES

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Sažetak

Uvod: *Tretman bolesnika koji boluju od raka, u smislu hemoterapije i radioterapije, značajno je evoluirao od svog početka. Obe terapije, naročito ako se koriste u kombinaciji, imaju veoma ozbiljan potencijal da dovedu do neželjenih efekata, koji narušavaju kvalitet života i potencijalno povećavaju mortalitet bolesnika obolelih od raka.*

Cilj rada: *U ovom radu opisan je uticaj radioterapije i hemoterapije na oralna tkiva. Oralne komplikacije koje se posledično javljaju mogu se svrstati u sledeće kategorije: mukozitis, kserostomija, gljivične, virusne i bakterijske infekcije, disgeuzija, disfagija, profuzno krvarenje, osteonekroza i mišićni trizmus.*

Zaključak: *Budući da je potreban širok spektar preventivnih i kurativnih mera, pojavljuje se potreba za sastavljanjem posebnih timova za brigu o bolesnicima pre, tokom i nakon radioterapije i hemoterapije. Takav onkološki tim trebalo bi imati doktora stomatologije, specijalistu oralne medicine kao aktivnog člana.*

Cljučne reči: *mukozitis, radioterapija, hemoterapija*

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Abstract

Introduction: *Cancer treatment, in terms of chemotherapy and radiotherapy has evolved significantly from its beginning. Both therapies, especially used in combination, had the potential to cause side effects, that potentially decrease in quality of life and lead to increased mortality rate in patients with cancer.*

The aim: *of the study: The effects of radiotherapy and chemotherapy were described. The oral complications which consequently occurred could be classified into following categories: mucositis, oral dryness, fungal, viral and bacterial infections, disgeusia, disfagio, profuse bleeding, osteonecrosis and muscle trismus.*

Conclusion: *Because of the wide range of preventive and curative measures, it is necessary to create a special team for caring of patients before, during and after radiotherapy and chemotherapy. In such case, dentist, oral medicine specialists should be an active member of oncology team.*

Key words: *mucositis, radiotherapy, chemotherapy*

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Uvod

Tretman bolesnika koji su oboleli od raka značajano je evoluirao u pogledu povećane efikasnosti i podnošljivosti od 1940. godine, kada su korišćeni antagonisti folne kiseline i azotni iperiti (citostatici) za lečenje leukemije i limfoma. Takođe, radioterapija je u upotrebi za lečenje bolesnika obolelih od raka više od 100 godina i napredovala je u smislu sofisticiranosti, efikasnosti i smanjenja neželjenih propratnih efekata. Međutim, oba tretmana, posebno ukoliko se koriste u kombinaciji jedan sa drugim, imaju veliki potencijal koji se ogleda u bolnim i iznurujućim neželjenim efektima koji jasno narušavaju kvalitet života bolesnika i potencijalno povećavaju mortalitet. Oralne komplikacije koje nastaju u toku tretmana ovakvih bolesnika su: mukozitis, kserostomija, gljivične, bakterijske i virusne infekcije, disgeuzija, disfagija, profuzno krvarenje, osteonekroza i mišićni trizmus. Mukozitis je inflamacija oralne mukoze koju uzrokuju jonizujuće zračenje i hemoterapija¹.

Epidemiološki podaci pokazuju da su uzroci smrtnosti u svetu: kardiovaskularna oboljenja (29%), infektivne bolesti (19%) i maligna oboljenja (13%)². Prevalencija malignih neoplazmi glave i vrata kod muškaraca je tri puta veća nego kod žena²⁻⁴. U poslednjih nekoliko decenija prevalencija preživljavanja bolesnika sa neoplazmama glave i vrata (usana, usne duplje, faringusa i laringsa) povećala se za 10%⁵. Terapeutske metode za lečenje malignih bolesti obuhvataju: hiruršku terapiju, radioterapiju, hemoterapiju, hormonsku terapiju, imuno-terapiju, kao i njihovu kombinaciju⁶.

Radioterapija

Radioaktivno zračenje koristi se u eksperimentalne, dijagnostičke i terapeutske svrhe. Jonizujući zraci deluju na najosetljivije delove ćelija – gene i enzimski sistem, pa nastaju funkcionalni i morfološki poremećaji koji indirektno izazivaju biohemijska oštećenja, stvarajući slobodne radikale i toksične produkte, koji povećavaju obim oštećenja. Najpre strada hemopoetični sistem, koji je najosetljiviji. Oralne promene mogu nastati nakon sekundarnog zračenja kod osoba koje u ustima imaju metalne protetske radove. Zbog toga je potrebno pre zračenja ukloniti metal i destruirane ili kariozne zube, koji su pripremani za ekstrakciju⁷.

Introduction

The treatment of cancer patients has evolved significantly in case of increased efficiency and tolerability from the year 1940, when the folic acid antagonist and nitrous iperites were used in treatment of leukemia and lymphoma. Also, the radiotherapy was used in the cancer treatment for more than 100 years and it progressed in terms of being sophisticated, efficient and the side effects were reduced. Both therapies, especially used in combination, have the potential to cause side effects, which potentially decrease the quality of life and lead to a potential increase in mortality rate in patients with cancer. The oral complications which consequently occurred could be classified into following categories: mucositis, oral dryness (xerostomia), fungal, viral and bacterial infections, dysgeusia, dysphagia, profuse bleeding, osteonecrosis and muscle trismus. Mucositis is inflammation of the oral mucosa which was caused by ionizing radiation and chemotherapy¹.

Epidemiological data showed that causes of death worldwide were cardiovascular diseases (29%), infectious diseases (19%), and malignant diseases (13%)². Men are about three times more likely than women to be diagnosed with the malignant head and neck cancer²⁻⁴. Survival from head and neck cancers (lip, oral cavity, pharynx, and larynx) has increased by 10% over the past few decades⁵. Therapeutic strategies for the treatment of malignant diseases include: surgical therapy, radiotherapy, chemotherapy, hormonal therapy, immunotherapy and combination of these therapies⁶.

Radiotherapy

Radioactive radiation is used for the experimental, diagnostic and therapeutic purposes. Ionizing radiation affects the most sensitive parts of cells – genes and enzymatic system, as well as the functional and morphologic disorders indirectly cause impairs of biochemical parameters by making free radicals and toxic products which increase the damage. Primarily, the most sensitive hematopoietic system has been destroyed. The oral changes may be found after secondary radiation of patients with metal prosthetic devices. Because of that, before radiation, it is necessary to remove the metal and badly decayed or damaged teeth⁷.

Radioterapija je primarna u terapiji karcinoma glave i vrata. Efekti terapije se, pored bolesnog tkiva, vide i na zdravom tkivu. Promene u usnoj duplji mogu biti rane i pozne. Rane promene javljaju se obično u toku prve nedelje i manifestuju se enantemom i edemom. U toku druge nedelje javljaju se erozije i ulceracije pokrivene sivožutim fibrinoznim eksudatom. Subjektivno se javljaju malaksalost, oralna suvoća i bolovi u toku govora i ishrane, kao i gubitak osećaja ukusa. Kada se zrače pljuvačne žlezde, osnovni problem je oralna suvoća. Spontano oporavljanje, nastaje nakon završene terapije. Pozne promene javljaju se nekoliko meseci nakon prestanka zračne terapije i eventualnog zarastanja oralnih lezija. Manifestuju se suvom i atrofičnom sluzokožom i floridnim cervikalnim karijesom, kao i pogoršanjem parodontopatije⁸.

Potencijalne oralne komplikacije uzrokovane radioterapijom mogu biti akutne i hronične. Akutne komplikacije uključuju mukozitis, kserostomiju, infekcije, disgeuziju, disfagiju i malnutriciju, dok su hronične komplikacije kserostomija, cervikalni karijes, teleangiektazije, miofibritis, trizmus, oštećenje vaskularizacije, nekroza mekih tkiva, osteoradionekroza, dentofacijalne malformacije (ukoliko je bolesnik izložen radioterapiji⁹ pre perioda adolescencije) i malnutricija⁹.

Hemoterapija

Hemoterapija je često korišćena kao pomoćni terapijski metod, zajedno sa radioterapijom ili kao metoda izbora kod transplantacije koštane srži. Hemoterapija, koja se daje za maligne lezije glave i vrata, može takođe uzrokovati promene na oralnoj mukozi. Lokalna sekundarna oralna infekcija, kao posledica mijelosupresije najčešća je komplikacija hemoterapije i može dovesti do sepse i smrtnog ishoda¹⁰. Druge komplikacije vezane za hemoterapiju su: disbalans elektrolita, hemoragija, akutna intoksikacija lekovima (uključujući povraćanje i mučninu), fotosenzitivnost, disfunkcija centralnog nervnog sistema, alopecija i malnutricija. Sonis i sar.¹¹ opisali su oralne komplikacije (mukozitis, ulceracije i kserostomiju) kod 40% bolesnika koji su lečeni standardnom hemoterapijom, a nisu imali malignitete vezane za region glave i vrata.

Radiotherapy is a primary treatment for head and neck cancer. The effects of the therapy, beside healthy tissue have been seen in damaged tissue. The changes in the oral cavity could be named as early and late. The early changes usually appear during the first week and manifested with enanthema and edema. During the second week, the erosions and ulcerations covered with grey-yellow fibrinous exudate may be present. Subjective fatigue, xerostomia and pain during talking and eating, as well as dysgeusia were found in these patients. When the salivary glands were under radiation, the main problem has been xerostomia. Recovering starts after the finished therapy. Late changes will appear several months after the finished radiotherapy and complete healing of oral lesions. These changes are manifested in dry and atrophic mucosa and florid caries, as well as in exacerbation of periodontal disease⁸.

The potential oral complication of radiotherapy could be an acute and chronic. Acute complications include: mucositis, infections, dysgeusia, dysphagia, and malnutrition, while the chronic complications are: xerostomia, cervical caries, telangiectasia, myofibritis, trismus, impaired vascularisation, necrosis of soft tissues, osteoradionecrosis, dentofacial malformation (the patient was exposed to radiotherapy as an adolescent) and malnutrition⁹.

Chemotherapy

Chemotherapy is often used in conjunction with radiotherapy like additional therapeutic method or like a choice method in the bone marrow transplantation. Chemotherapy, for the malignant head and neck lesions, can cause alteration of the oral cavity mucosa. Local secondary oral infection, as a consequence of myelosuppression, is the most frequent complication of chemotherapy, and could lead to the septic shock and death¹⁰. Other chemotherapy side effects are: electrolyte imbalance, hemorrhage, acute drug intoxication (including vomiting and nausea), photosensitivity, central nervous system dysfunction, alopecia and malnutrition. Sonis et al.¹¹ described the oral complications (mucositis, ulcerations and xerostomia) in 40% of all patients who received standard chemotherapy, and they had no malignant head and neck lesions.

Oralne komplikacije prijavljene su kod 75% bolesnika, koji su na visokim dozama hemoterapeutika, 70% do 80% bolesnika kojima je presađena koštana srž i 100% bolesnika koji primaju radioterapiju za malignitete glave i vrata¹². Hemoterapeutici imaju uticaj na koštanu srž i dovode do smanjenja mijeloproliferacije, što ima za posledicu, između ostalog, trombocitopeniju, leukopeniju i neutropeniju. Ovi agensi takođe izazivaju promene na oralnoj mukozi, koje se manifestuju kao smanjenje mitotičke aktivnosti oralnih epitelnih ćelija, što za posledicu ima epitelnu atrofiju, smanjenu otpornost epitela na mehaničke iritacije, mukozitise i oralne ulceracije^{12,13}. Ulceracije obezbeđuju slobodan prolaz sekundarnoj infekciji, zbog virulentnih mikroorganizama oralne flore. Prisustvo neutropenije može dovesti do sepse i njenih ozbiljnih komplikacija, pa i do smrtnog ishoda.

Stomatolog u onkološkom timu

Onkološkom timu potreban je doktor stomatologije da bi mogao da ublaži komplikacije koje su posledica teške akutne radioterapije i spreči razvoj hroničnih komplikacija¹⁴⁻¹⁶.

Bolesnici koji su planirani za zračnu terapiju glave i vrata ili oni koji primaju hemoterapiju moraju se podvrgnuti stomatološkom pregledu i tretmanima koji su podeljeni na one koje se izvode pre, u toku i nakon radioterapije i hemoterapije.

Procedure koje se izvode pre radioterapije ili hemoterapije

- oralni klinički pregled zuba i vilica x-zračenjem (ortopantomografija ili retroalveolarno snimanje zuba);
- edukacija bolesnika, instrukcije i motivacija za održavanje višeg nivoa oralne higijene pre, u toku i nakon terapije; agresivni protokol o održavanju oralne higijene;
- kompletno i temeljno lečenje svih zuba obe vilice;
- radikalni pristup lečenju zuba;
- ekstrakcija svih zuba koji nemaju prognozu opstanka dužu od 5 godina;
- indikacije za ekstrakciju su: avitalni zubi, zubi sa apikalnim paradontitisom, zubi koji zahtevaju endodontski tretman, zubi sa džepovima dubljim od 6 mm i vidljivim furkacijama, sa destruiranim kronicama i zaostalim korenovima korenima zuba, impaktirani zubi i zubi koji su povezani sa tumorom⁶;

Oral complications were reported in 75% of all patients who were receiving high dose of chemotherapy, in 70%-80% of all patients who were undergoing bone marrow transplantation and in 100% of patients who were receiving radiotherapy for malignant head and neck lesions¹². Chemotherapeutics have an impact on bone marrow and lead to impaired myeloproliferative activity, which consequently lead to the thrombocytopenia, leucopenia and neutropenia. These agents also cause the changes on oral mucosa, which manifest thought impaired mitotic activity within oral epithelial cells, and consequently lead to epithelial atrophy, impaired epithelial activity on the mechanical irritations, mucositis and oral ulcerations^{12,13}. The ulcerations provide free entrance for secondary infections, caused by virulent microorganisms of oral flora. The presence of neutropenia may lead to septic shock and their severe complications, as well as lethal outcome.

A dentist on the oncology team

The oncology team needs a dentist who would reduce complication appearing as a consequence of severe acute radiotherapy and stop the development of further chronic complications¹⁴⁻¹⁶.

Patients who were planned for radiotherapy of head and neck or they who received chemotherapy should have dental check up and treatments which are divided before, during and after radiotherapy and chemotherapy.

The procedures performed before undergoing radiotherapy and chemotherapy

- the clinical oral examination of teeth and jaw by dental X-rays (orthopantomography and retroalveolarradiography);
- education of patients, instructions and motivation for improving oral hygiene methods before, during and after therapy; more aggressive protocol for maintaining good oral hygiene;
- complete and thorough dental treatment of both jaws;
- radical dental treatment approaches:
- extraction of the teeth with survival rates no higher than 5 years;
- indications for extraction: avital teeth, teeth with apical peridontitis, teeth that

- kod bolesnika kod kojih je zakazana radioterapija i hemoterapija, ekstrakcija zuba izvodi se 14 –20 dana (minimum 10 dana) pre terapijske procedure;
- ekstrakcionu ranu ne bi trebalo ostavljati sa oštrim ivicama alveolarne kosti, tako da bi trebalo izvesti alveoloplastiku nakon ekstrakcije zuba;
- nakon ekstrakcije zuba, ranu treba ušiti kako bi ona zarasla “*per primam*”; svež koagulum je osjetljiv na radijaciju;
- režim davanja antibiotičke terapije posle ekstrakcije zuba isti je kao kod bolesnika sa infektivnim endokarditisom, sa mogućim produženjem terapije¹⁷;
- potrebno je odraditi cistektomiju, ukoliko su prisutne ciste u vilicama;
- mobilne proteze ne treba nositi tokom zračne terapije i duže vreme posle toga; mobilne proteze mogu se nositi samo tokom jela i prilikom socijalnih kontakata, uz odobrenje i redovne kontrole stomatologa;
- individualni splint za aplikaciju 1% gela fluora mora biti urađen.

Procedure koje se izvode u toku radioterapije i hemoterapije:

- kontrola mukozitisa (ultra meka četkica za zube, zubni konac za higijenu interdentalnih prostora bez provokacije krvarenja, hlorheksidin, lokalna aplikacija 1% sodium-fluoridnog gela korišćenjem specijalno dizajniranog individualnog splinta);
- kontrola bola (lokalni anestetici u obliku gela);
- prevencija sekundarne infekcije (pranje usta nekoliko puta dnevno pomoću miksture sode bikarbone i kuhinjske soli, hlorheksidina, nistatina i mikonazola).

Procedure koje se izvode nakon radioterapije i hemoterapije:

- sav trud treba se usmeriti na oralnu negu zuba, gingive, oralne mukoze i faringosa^{18,19};
- zube treba prati mekom četkicom nakon svakog obroka i pre spavanja;
- treba koristiti paste na bazi fluora;
- vratove zuba (cervikalni karijes) i interdentalne prostore treba održavati pomoću interdentalnog konca i interdentalnih stimulatora, međutim ne sme se provocirati gingivalno krvarenje;

- require endodontic treatment, teeth with pockets deeper than 6 mm and visible furcations, teeth with destructed crowns and radices relictae, impacted teeth and teeth associated with the tumor⁶;
- in patients undergoing radiotherapy and chemotherapy, appointed tooth extraction was performed 14–20 days (minimum 10 days) before therapeutic procedure;
- an extraction wound should not be left with sharp edges and alveoloplasty of the alveolar bone should be performed after tooth extraction;
- after tooth extraction, the wound should be sutured to heal “*per primam*”, the fresh blood coagulum is sensitive to radiation;
- the antibiotic treatment regimes after tooth extraction is the same as well as in patients with infective endocarditic, with potential treatment elongation¹⁷;
- cystectomy is to be performed, if the cysts are found in the jaws;
- the mobile dental prosthesis should not be worn during radiotherapy and for a long time after; mobile dental prosthesis may be worn during eating and social contact, with the approval and regular dental checkups;
- an individual splint used for application of fluoride 1% dental gel should be done.

The procedures performed during undergoing radiotherapy and chemotherapy:

- control of oral mucositis (ultra soft tooth brush, dental floss for interdental spaces without bleeding provocation, chlorhexidine, local application of 1% of sodium fluoride gel used with specially designed individual splint);
- the pain control (local anesthetic dental gel); and
- preventing of a secondary infection (several times per day using of mouthwash of baking soda and table salt, nystatin and miconazole).

The procedures performed after undergoing radiotherapy and chemotherapy:

- all efforts should be put into maintaining a good oral hygiene of teeth, gingiva, oral mucosa and pharynx^{18,19};
- the teeth should be brush with a soft brush after every meal and before sleeping;
- the fluoride toothpaste should be used;

- usta treba ispirati nekoliko puta dnevno rastvorom kuhinjske soli sa dodatkom sode bikarbone;
- post-radijaciona kserostomija je česta komplikacija; ovim bolesnicima trebalo bi dati sledeća uputstva: tegobe će biti blaže ukoliko pijuckate neko hladno piće; preporučuje se da se maslinovim uljem sa sokom od limuna ispere usna duplja²⁰;
- treba koristiti veštački slani rastvor (Glandosane sprej, Oral Balance gel, Xero-Lube);
- mogu se propisati stimulatori pljuvačke (rastvor pilokarpin-hidrohlorid Salagen tablete);
- vitaminske kreme (d-pantenol) (konstantno oblagati usne njima);
- kontrolne posete stomatologu, minimum jednom u tri meseca.

Komplikacije na maksili i mandibuli uzrokovane radioterapijom (osteonekroza)

Komplikacije na maksili i mandibuli predstavljaju specifičan problem sa kliničkom slikom osteomijelitisa, i osteonekroze nakon zračne terapije i sekvestracije²¹. Rizik od ovih komplikacija značajno je smanjen ukoliko se koriste odgovarajuće zaštitne mere pre zračne terapije. Međutim, zračna terapija smanjuje regenerativnu sposobnost kostiju, oštećuje interkoštani protok krvi i smanjuje broj osteocita i osteoklasta. Rizik je veći ukoliko se vadi zub u polju koje je bilo ozračeno. Promene su često praćene limfedemom. Mandibula je znatno osetljivija u odnosu na maksilu.

Sledeće mere su predložene ukoliko se javne neke od ovih komplikacija:

- visoke doze antibiotika prema antibiogramu. Oksigenacija u hiperbaričnoj komori da bi se povećala oksigenacija tkiva, što stimuliše angiogenezu, funkciju osteoblasta i fibroblasta²²;
- kritičko razmatranje hirurške terapije ukoliko ne postoji sekvestracija.

- tooth cervices (cervical caries) and interdental spaces need to be cleaned by interdental floss and interdental stimulators, however gingival bleeding should not be provoked;
- the mouth should be rinsed few times per day by using solution of table salt and baking soda;
- radiation-induced xerostomia is a frequent complication: these instructions should be explained to the patient: the symptoms may be milder if you drink cold drink; it is recommended to rinse mouth by olive oil with lemon juice²⁰;
- the artificial saline solution should be used (Glandosan spray, Oral Balance gel, Xero-Lube);
- the salivary stimulants may be prescribed (solution of pilocarpine-hydrochloride, Salagen tablets);
- vitamin creams (d-panthenol) (applying lip products repeatedly); and
- regular dental check-ups, minimum one per three months.

Complications in the maxilla and mandible caused by radiotherapy (osteonecrosis)

Complications in the maxilla and mandible represent specific problem of radiotherapy-induced clinical signs of osteomyelitis, osteonecrosis and sequestration²¹. The risk of these complications is significantly reduced if the protective measures are properly used before radiotherapy. However, radiotherapy reduces the ability to regenerate bone, impairs intercostal blood flow through blood vessels and reduces number of osteocytes and osteoblasts. The risk is higher if the tooth extraction is in the area of radiation. The changes are frequently associated with lymphedema. The mandible is noticeably more sensitive as compared to the maxilla.

The following measures are suggested if some of these complications occur:

- High doses of antibiotic according to the antibiogram. Oxygenation in hyperbaric chamber to increase tissue oxygenation, which stimulates angiogenesis, osteoblasts and fibroblasts function²²; and
- A critical consideration of the surgical treatment, if there is no sequestration.

Mukozitis

Oralni mukozitis predstavlja inflamaciju sluzokože usne duplje uzrokovanu radio-terapijom i hemoterapijom. Oralni mukozitis pogoršava kvalitet života bolesnika. Uzimanje hrane i pića je teško, a nekada je čak neizvodljivo, što vodi malnutriciji i dehidraciji.

Komunikacija je otežana zbog bolnih lezija²³⁻²⁵. Kliničko vrednovanje mukozitisa predstavljeno je prema kriterijumima Svetske zdravstvene organizacije modifikovaniod strane Scully i sar.²⁶ (Tabela 1).

Oralni mukozitis predstavlja promenu epitela usne duplje u vidu eritema, erozija, ulceracija i deskvamacija (Slika 1).

Promene se mogu podeliti, prema WHO klasifikaciji, na sledeći način:

1. Lokalizovani eritem bez bola;
2. Generalizovani eritem bez bola, ili lokalizovani eritem sa ulcerom i slabim bolom < 20%;
3. Generalizovani eritem sa brojnim ulceracijama i umerenim bolom pri uzimanju čvrste hrane;
4. Generalizovani eritem sa brojnim ulceracijama, praćen jakim bolom pri uzimanju tečne hrane.

Mukozitis počinje trećeg dana, a maksimum dostiže dvanaestog do četrnaestog dana zračne terapije i hemoterapije. Tkivne promene rezultat su delovanja terapije na enzimski sistem, DNK, RNK i stvaranje slobodnih radikala koji remete ćelijski genetski materijal, stvarajući ćelije mitotički inkompetentne ili uzrokujući programiranu ćelijsku smrt – apoptozu. To rezultira poremećajem keratinizacije, atrofijom epitela, atrofijom i degeneracijom kolagenih vlakana, vaskularnim promenama, ulceracijama i nekrozom⁸.

Mucositis

Oral mucositis represents inflammation of oral mucosa caused by radiotherapy and chemotherapy. Oral mucositis decreases the patients' quality of life. Taking food and drinks is difficult and sometimes even impossible, and can lead to malnutrition and dehydration. Communication is difficult because of painful lesions²³⁻²⁵. Clinical assessment of mucositis is represented by criteria of World Health Organization (WHO), modified by Scully et al.²⁶ (Table 1).

Oral mucositis represents the change of epithelium of oral cavity in form of erosions, ulcerations and desquamations (Figure 1).

The changes can be divided according to WHO classification into:

1. Local erythema without pain symptoms
2. Generalized erythema without pain symptoms, or local erythema with ulceration and mild pain <20%
3. Generalized erythema with multiple ulcerations and moderate pain during taking a solid foods
4. Generalized erythema with multiple ulcerations associated with severe pain during taking liquid foods.

Radiotherapy and chemotherapy induce oral mucositis which starts on the third day, but reaches its maximum on the twelfth to fourteenth day. Tissue changes are a result of the therapy impact on DNA, RNA and free radicals which disturbed genetic material, by making mitotic incompetent cells, or cause process of programmed cell death-apoptosis. That results in disturbed keratinization, atrophy and degeneration of collagenous fibers, vascular changes, ulcerations and necrosis⁸.

Tabela 1. Kliničko vrednovanje mukozitisa
Table 1. Clinical assessment of mucositis

Gradus Grade	Klinički izgled Clinical signs
0	Nisu prisutne lezije mukoze Oral mucosa lesions were absent.
1	Osetljivost mukoze – blag eritem Oral <i>mucosal sensitivity</i> –mild erythema
2	Eritem/-ulceracije, moguće uzimanje čvrste hrane Erythema-ulcerationes, possible eating solid foods
3	Teške ulceracije i eritem – dijeta koja podrazumeva unošenje isključivo tečne hrane Big ulcerations and erythema – diet with liquid food
4	Nekroza i krvarenje–hranjenje preko usne duplje Necrosis and bleeding – taking food <i>through the mouth</i> is impossible



Slika 1. Mukozitis, gradus II i *Pseudomembranous candidiasis*
Figure 1. Mucositis, Gradus II and *Pseudomembranous candidiasis*

Terapija oralnog mukozitisa

Terapija oralnog mukozitisa obuhvata široki spektar lekova i procedura: lokalni anestetici, kortikosteroidi, sistemski analgetici, sistemski ili lokalni antiinflamatorni lekovi, antiseptici, antibiotici, orabaze, keratinocitni faktor rasta (stimuliše proliferaciju i diferencijaciju epitelnih ćelija), interferon, Lysobact, miks fiziološkog rastvora i sode bikarbone, veštačka pljuvačka i različiti čajevi.

Bolesnici sa lošom oralnom higijenom i karijesnim zubima imaju veću učestalost mukozitisa i teže kliničke simptome, nego bolesnici sa dobrom oralnom higijenom i popravljenim zubima.

Kserostomija

Otok i bol pljuvačnih žlezdi, uz smanjeno lučenje pljuvačke, koja je gusta i lepljiva, javljaju se već nekoliko sati nakon zračenja. Ove tegobe, u većini slučajeva, prestaju za nekoliko dana²⁷. Nakon par dana primene radioterapije dolazi do oštećenja seroznih acinusa pljuvačnih žlezda, pa je pljuvačka viskozna. U daljem toku radioterapije oštećuju se i mukozne ćelije acinusa pljuvačnih žlezda, pa je smanjen ukupan volumen izlučene pljuvačke. Ukoliko je došlo do trajnog i ireverzibilnog funkcionalnog oštećenja parenhima pljuvačnih žlezda, nastaje kserostomija²⁷.

Iako vrednosti radiotolerantne doze za parotidnu žlezdu nisu precizno definisane, Emami i sar.²⁸ su, na osnovu rezultata brojnih studija i kliničkog iskustva, zaključili da vrednosti doza koje dovode do rizika pojave kserostomije, od 5% do 50% u toku 5 godina od sprovedenog zračenja, iznose 32 Gy i 46 Gy, a da kod skoro svih bolesnika čije su parotidne pljuvačne žlezde u celosti ozračene dozom od 50 Gy do -60 Gy, dolazi do kompletnog i ireverzibilnog prestanka lučenja pljuvačke²⁹. Dozom od 50-60 Gy, dolazi do kompletnog i ireverzibilnog prestanka lučenja pljuvačke²⁹.

The oral mucositis therapy

The oral mucositis therapy protocol includes wide range of drugs and procedures: local anesthetics, systemic or local anti-inflammatory drugs, antiseptic drugs, antibiotics, keratinocyte growth factor (stimulates proliferation and epithelial cells differentiation), interferon, Lysobact, mix of saline solution and baking soda, artificial saliva and different types of tea.

The higher percentage of mucositis and severe clinical symptoms could be found in patients with poor oral hygiene and dental decay, than in patients with good oral hygiene and dental fillings.

Xerostomia

Swelling and pain in the salivary glands, together with reduced secretion of the saliva, which is thick and sticky, manifest as soon as few hours after the radiotherapy. In most cases, these symptoms disappear in a few days²⁷. The serous acini of salivary glands damage occur a couple of days from the start of radiotherapy, and the saliva becomes viscous. In the further course of radiotherapy, mucous cells of salivary gland acini get damaged so the total volume of saliva is reduced. In the case of complete and irreversible functional damage of salivary glands parenchyma, xerostomia is manifested²⁷.

Although radiotolerance dose values for parotid gland are not precisely defined, Emami et al.²⁸ concluded, based on results of numerous studies and clinical experience, that dose values which cause xerostomia from 5% to 50% during 5 years from being under radiotherapy were 32Gy and 46Gy, and in patients where salivary glands were under radiotherapy from 50-60Gy came to complete and irreversible stopping of saliva production²⁹.

Disgeuzija

Disgeuzija, se odnosi na poremećaj osećaja ukusa i čest je klinički problem sa kojim se susreću bolesnici oboleli od raka³⁰. Prema nekim procenama, 50% – 75% bolesnika obolelih od raka, koji primaju zračnu terapiju ili hemoterapiju, ili oba, imaju disgeuziju³¹. Interesantno je to da bolesnici na zračnoj terapiji (uglavnom glave i vrata) imaju goru disgeuziju nego bolesnici na hemoterapiji. Težina ovog oboljenja u korelaciji je sa kumulativnom dozom zračenja. Ustvari, 15% bolesnika na zračnoj terapiji ima poremećen osećaj ukusa nakon završetka njihovog tretmana³¹. Etiologija disgeuzije je multifaktorijalna, ali postoje jednostavni tretmani, uključujući savetovalište o ishrani i lečenje oralne infekcije, koji bi se smanjili loš uticaj ovog oboljenja na kvalitet života bolesnika³². Za lečenje idiopatske disgeuzije neke studije predlažu preparate cinka, konkretno u studiji Halyard i sar.³³ koristili su cink-glukonat, koji je poboljšao osećaj ukusa, apetit i raspoloženje bolesnika. Fink i sar.³⁴ predlažu vitamin D, kao suplement u terapiji ove oralne komplikacije.

Oralna kandidijaza

Candida albicans je gljivica koja je komensal i u normalnim uslovima koezistira u usnoj duplji sa drugim oralnim mikroorganizmima i ne uzrokuje oboljenje. Kolonizacija i infekcija dešavaju se kada su sistemski ili lokalni faktori oštećeni, uključujući imunosupresiju, hiposalivaciju, oštećenje tkiva i / ili poremećaje flora, kod obolelih od raka koji su pod terapijom. U pregledu literature Lalla i sar.³⁵, procenat bolesnika obolelih od gljivičnih infekcija, koji su inače podvrgnuti hemoterapiji i zračnoj terapiji glave i vrata, bio je 7,5% pre tretmana, 40% tokom tretmana, i 30% nakon tretmana. Pseudomembranozna kandidijaza (Slika 1), hronična (atrofična) eritematozna kandidijaza i angularni heilitis najčešće su kliničke forme ovog oboljenja, dok je hronična hiperplastična forma (nodularna kandidijaza) retko prijavljena.

Dysgeusia

Dysgeusia is a taste disturbance and it is a frequent clinical symptom in cancer patients³⁰. According to some estimates, 50% to 75% of cancer patients who receive radiotherapy or chemotherapy or both have dysgeusia³¹. It is interesting that patients undergoing radiotherapy (mostly head and neck) have greater risk of dysgeusia than patients undergoing chemotherapy, the severity of disease is in correlation with cumulative radiation dose. Actually, 15% of patients undergoing radiotherapy have taste disturbances after the end of their treatment³¹. Etiology of dysgeusia is multifactorial, but the treatment is simple, includes nutrition counseling and treating of oral infection to decrease the negative impact of this disease on the quality of life of patients³². For treating of idiopathic dysgeusia some studies recommend zinc supplements; specifically in their study, Halyard et al. used zinc gluconate, which improved taste sensation, appetite and mood of patients³³. Fink suggests vitamin D, as supplement in the treatment of this oral complication³⁴.

Oral candidiasis

Candida albicans is a fungus, which is commensal and in normal circumstances coexists with other microorganisms in oral cavity not causing disease. Colonization and infection occur when systemic and local factors are impaired, including immunosuppression, hyposalivation, tissue damage and/or disturbed flora in patients undergoing cancer therapy. Lalla et al.³⁵ found that percent of candidiasis in patients undergoing chemotherapy and radiotherapy for head and neck were 7.5% before treatment, 40% during treatment and 30% after treatment. Pseudomembranous candidiasis (Figure 1), chronic (atrophic) erythematous candidiasis and angular cheilitis are the most frequent clinical forms of this disease, while the chronic hyperplastic form (nodular candidiasis) is rarely reported.

Virusne infekcije

Oralne virusne infekcije, uključujući *herpes simplex virus (HSV)*, *varicella zoster virus (VZV)*, Epstein–Barr virus (EBV) i cytomegalovirus (CMV), česte su komplikacije kod bolesnika obolelih od raka. Teške infekcije mogu dovesti do dehidracije, malnutricije i komplikacija opasnih po život, uključujući encefalitis i diseminovanu infekciju. Kod imunokompromitovanih bolesnika ispoljavanje HSV može biti atipično i može se pomešati sa mukozitisom i aftoznim stomatitisom.

U najvećem broju slučajeva, HSV infekcija je rezultat reaktivacije virusa. Elad i sar.³⁶ su zabeležili prevalenciju HSV infekcije kod neutropeničnih bolesnika tokom tretmana hematoloških maligniteta u oko 50% slučajeva. Kod bolesnika koji su na zračnoj terapiji glave i vrata HSV je zastupljen 0%. Kod bolesnika koji su kombinovali radioterapiju i hemoterapiju zastupljenost je blizu 40%. Ovi podaci pokazuju da je imunosupresija zbog hemoterapije glavni faktor HSV infekcije. Neutropenični bolesnici sa hematološkim malignitetima izloženi su najvećem riziku.

Vlasasta leukoplakija je, česta manifestacija Epstein–Barr virusa koja se viđa kod HIV pozitivnih bolesnika. Primarno se nalazi na bočnim stranama jezika, mada i druge površine jezika mogu biti zahvaćene: dorzalna i ventralna površina jezika, bukalna mukoza ili gingiva. Može se pomešati sa hroničnom hiperplastičnom kandidijazom. Javlja se kod bolesnika obolelih od raka, zbog imunokompromitovanog domaćina. Zabeležena je kod bolesnika sa akutnom mijeloidnom leukemijom, akutnom limfocitnom leukemijom i multiplim mijelomom, koji su podvrgnuti hemoterapiji³⁷⁻³⁹, kao i kod bolesnika sa stromalnim gastrointestinalnim tumorom⁴⁰, koji su na pronizonu.

Bakterijske infekcije

Normalnu oralnu floru čine mnoge bakterije, koje mogu postati patogene kod imune supresije. Rautemaa i sar.⁴¹ tvrde da *Viridans streptococci*, *Prevotellae*, *Fusobacterium*, *Actinobacillus actinomycetemcomitans* i *Actinomyces* vrste mogu biti uzrok oralne mukozne infekcije. Takve infekcije su obično lokalizovane i mogu biti lečene kombinacijom penicilina i metronidazola.

Viral infections

Oral viral infection including *herpes simplex virus (HSV)*, *varicella zoster virus (VZV)*, Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are the most frequent complications in patients with cancer. Severe infections could lead to dehydration and malnutrition and life-threatening complication including encephalitis and disseminated infection. In immunocompromised patients, presentation of HSV could be atypical and could be mixed with mucositis and aphthous stomatitis.

In most cases, HSV infection is a result of virus reactivation. Elad et al.³⁶ recorded prevalence of HSV infection in nearly 50% of neutropenic patients during cancer hematologic treatment. In patients under radiotherapy for head and neck prevalence of HSV was 0%. In patients under radiotherapy and chemotherapy prevalence was nearly 40%. These data showed that immunosuppression caused by chemotherapy was the main factor of HSV infection. Neutropenic patients with hematologic malignancies were classified in the highest risk category.

Hairy leucoplakia, frequent manifestation of Epstein–Barr virus, is seen in HIV positive patients. Primarily, it is found on the sides of the tongue, although other surfaces of the tongue can be affected, like dorsal and ventral surface of the tongue, as well as buccal mucosa and gingiva. It can be substituted with chronic hyperplastic candidiasis. It is found in cancer patients because of the immunocompromised host. It has been reported in the patients undergoing chemotherapy with acute myeloid leukemia, acute lymphocyte leukemia and multiple myeloma³⁷⁻³⁹, as well as in patients with a stromal gastrointestinal tumor receiving prednisone⁴⁰.

Bacterial infections

Normal oral flora contains different types of bacteria, which can become pathogenic under immunosuppression. Rautemaa et al.⁴¹ claim that *Viridans Strep*, *Prevotellae*, *Fusobacterium*, *Actinobacillus actinomycetemcomitans* and *Actinomyces* species can be cause of oral mucosal infections. Usually, such infections can be localized and treated only with combination of penicillin and methronidazol.

Karijes zuba

Zabeležena je prevalencija od približno 6% inficiranih zuba / apcesa tokom hemoterapije⁴². Bolesnici koji su bili na zračnoj terapiji zbog maligniteta glave i vrata imali su veći procenat pokvarenih / ekstrahiranih/plombiranih zuba nego bolesnici koji su bili na antineoplastičnoj terapiji. Rautemaa i sar.⁴¹ predložili su upotrebu proizvoda koji sadrže fluorimid i vodice za ispiranje koje sadrži hlorheksidin.

Zaključak

Uprkos značajnim poboljšanjima u tretmanu bolesnika obolelih od raka, oralne komplikacije su česte i dovode do nelagodnosti, pogoršanja kvaliteta života i povremeno do teških malnutricija i infekcija, koje su problemi opasni po život ovih bolesnika. Mada, postoje uspešne terapijske metode koje mogu da ublaže ove tegobe, potrebna su dalja istraživanja koja će uticati na njihovo poboljšanje i koja će imati za cilj smanjenje neželjenih efekata radio-terapije i hemoterapije bolesnika obolelih od raka. Onkološki tim bi trebalo da uključi doktora stomatologije radi prevencije i tretmana oralnih komplikacija pre, nakon i posle zračne terapije i hemoterapije.

Konflikt interesa

Autori nemaju nikakvu finansijsku korist ili sukob interesa.

Tooth decay

The prevalence is reported to be approximately 6% of the tooth infection/abscess during chemotherapy⁴². Patients undergoing radiotherapy for head and neck malignancies have a larger percentage of teeth decay/extracted/seal teeth than patients undergoing antineoplastic therapy. Rautemaa et al.⁴¹ suggest using of fluoride products and chlorhexidine mouthwash.

Conclusion

Despite significant improvements in treatment of cancer patients, oral complications are frequent and lead to discomfort, decrease in the quality of life and sometimes severe malnutrition and infections which are life-threatening. Although successful therapeutic methods can reduce these problems, further research is necessary for improvement of the quality of life and reduction of side effects of radiotherapy and chemotherapy in cancer patients. The dentist should be an active member of oncology team for prevention and treatment of oral complications, before, during and after radiotherapy and chemotherapy.

Conflict of interest

The authors have no any financial benefit or conflict of interests.

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