Management of oral cavity disorders during chemotherapy in oncologic patients

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Summary
Chemotherapy is an important part of modern methods for treatment of oncologic diseases. As any medication or method, the chemotherapeutical agents also have complications and side effects, from which our interest is the changes in oral cavity during and after of cancer treatment. By using of chemotherapeutic agents, the majority of patients may develop the complications of the oral health. The literature describes mucosits, oral pain, infection, hemorrhages, xerotomy, neurological and nutritional problems. Each of them is a potential threat to the patient's general condition, according to chronological or dental age - for oral hard or soft tissues. These factors will cause significant violations in future permanent dentition, also problems – such dysphagia, dysphonia, development of oral organs and face. Unfortunately, in literature there is less information about the condition of pediatric patients, which are subject of chemotherapy for oncologic diagnosis. Accordingly, there is less information about maintaining the conditions for facilitating prevention of dangerous changes and for the development of future permanent dentition. The goal of the research is to find information about frequency and quality of the damage in oral cavity caused by chemotherapy in oncologic pediatric patients. Also, to develop the special methodology regarding to avoid and prevent vulnerability of the child's health condition because of pathological changes in oral cavity.

Key words: *cancer, oral cavity, chemotherapy, disorders*

Introduction

The chemotherapy takes important place among the modern treatment methods of oncologic diseases. The meaningful results are also achieved with combination of chemo- and radiotherapy (f.e. cancer of facial and neck region) [1]. Unfortunately, as any method or medicament, chemotherapy also has its complications and side effects, from which particularly complications in oral cavity are the space of our interest. These complications mainly reducing quality of painless life potential, which by itself reduces the quality of living and increases potential of death [2].

During the chemotherapy there is risk to get the oral cavity health complications. In literature is described mucositis, pain, infection, haemorrhagie, xerostomy, problems of neurological characteristic and complications with feeding [3].

Chemotherapy Agents and Their Side Effects

Some chemotherapy agents are characterized by complications in oral cavity. Among of them mainly aggressive are:

Metotrexate

Metotrexate is used for treatment of some kind of cancers, also for controlling of severe psoriasis and rheumatoid arthritis, which are not treatable with other medicaments. Metatroxate is antimetabolic drug, may be used for controlling juvenile rheumatism, it is influencing on process of cell growing and depressing of immune system.

Complications: drowsiness and dizziness, temporary hair loss may occur, infection risk (sometimes fatal). Rarely, but still may occur allergic reactions on mentioned medicament (rush, itching, swelling – face, tongue, throat, sever dizziness, complicated breathing), also – vomiting, nausea, xerostomia, stomach pain [4].

Cytarabine

Cytarabine for injection (trade name: Cytosar-U, Tarabine PFS) is the chemothich may have fatal be the reason of fatal ve specialy d ia, y of lifeing with oid arthritiserapy agent, used for treatment of special type tumors – acute lymphoblastic leukemia (ALL). Main side effects of Cytarabine are classified as vomiting and nausea, loose of appetite, diarrhea, meteorism, headache, dizziness, drowsiness, ataxia, Memory worsening, pain; on the place of injection – pain, swelling, rediness [5].

Fluorouracil

Fluorouracil (trade names: Adrucil ®, 5-Fluorouracil, 5-FU) is anticancer ("antineoplasmatic" or "cytotoxic") chemotherapeutic agent, it is classified as an antimetabolic drug. Indications for use: Large intestine and rectal cancer, breast cancer, gastrointestinal cancer: rectum, esophagus, pancreas and stomach cancers, head and neck region cancer, unknown primary (Square Cell) cancer, neuroendocrine tumors, thymus cancer, uterine cervix cancer, bladder tumor, hepatoid cancer. Used for topical appling (cream or solution) in the case of skin tumors and active keratosis, basal cellular cancer.

Side effects: diarrhea, nausea, stomatitis, decrease appetite, eyes tears, photophobia, taste change, metal taste during infusion, it can cause increased risk of infection, anemia, and / or bleeding. Skin reactions: dryness, xerodermia, hyperpigmentation, hair thinning, nail changes - bleaching, loss of nails (rarely). Palmar-plantar erythrodesia or PPE - skin rash, swelling, redness, pain. Serious adverse reactions on Fluorouracil: chest pain, ECG changes and increased heart enzymes [6].

Thioguanine
Trade names: Tabloid®, other names: 6-TG, 6-Thioguanine, 2-Amino-6-Mercaptopurine.
Tiaguanin is a chemotherapy agent ("antineoplastic" or "cytotoxic"). Tioginin is classified as antimetabolic drug. It is used for treatment of acute myelogenic leukemia (AML), acute lymphoblastic leukemia (ALL).

Side effects: ɔnemia, which can cause increased risk of infection and bleeding. Edema of the extremities, nausea (usually small), bad appetite. Violation of liver functions, tumor lysis syndrome is available – it is permitted as a result of leukemia treatment which can cause renal insufficiency. Tumor lysis syndrome usually occurs within 24-48 hours. Treatment - hydration, medication Alopurinol, which blocks the urea in blood.

Tioguanin itself is potentially carcinogenic medication, which can increase the risk for secondary cancer development. Long-term use of this drug is associated with the risk of secondary cancer. Pain during swallowing, mucous ulcers may be manifested [7].

Actinomycetin-D (Dactinomycetin)
Actinomycin D (Dactinomycin) is a chemotherapeutic agent that is used to treat certain types of cancer. Actinomycin D (Dactinomycin) prevents the growth of cancer cells, which eventually are destroyed.
The most common side effects include nausea and vomiting. Decrease of bone marrow function: anemia, bruises or bleeding, high risk of infections, hair loss; Loss of appetite, difficulties for mealing, weight loss. Fever. Diarrhea or stomach pain; Changes in the liver functions. Acute allergic reaction: redness, dizziness, headaches, and breathing difficulties. Oral side complications: mucositis [8].

Amsacrine
Amsidine® is a chemotherapeutic agent that is used in the treatment of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). It also can be used for other cancer treatment. Serious and life-threatening side effects: the risk of infection, neutropenia. Bleeding and hemorrhagies - due to variance of vascular velocity and thrombocytopenia. The urea in the blood. Anemia, fatigue, respiratory failure [11].

Bleomycin
Trade name: Blenoxane ® Bleomemycin is a chemotherapeutic agent that is used for treatment of oncologic diseases. In particular, it belongs to class of antitumor antibiotics. This medication is produced on base of Streptomycetes fungies.
Bleomycin stops or slows down the growth and development of cancer cells and the reproductive process of mentioned cells in different phases. exact dose and schedule of treatment depends on the type of cancer, the cancer response to the medication, the patient's height, weight, general health condition and other factors. Side effects: allergy, redness, inflammation, dermatitis, rash, hair loss; Vomiting, loss of appetite, weight loss; Suddenly weakness of limbs on one side, confusion, difficulty of speech, sudden dizziness, loss of coordination, severe headache, chest pain, decreased urination. Changes in the oral cavity during treatment: the ulcers on oral mucosa and tongue [9].

Doxorubicin
Doxorubicin is a cytotoxic, anthracycline, topoizomerase II inhibitor, which is indicated as a component of a multicomponent chemotherapy course.
Indication for administration is the breast cancer related to the primary recreational lymph node. Doxorubicin is also shown as agent to treat ovarian, prostate, stomach, thyroid cancer; Lung tumors, small hepatic cancer, gastrointestinal cancer, head and neck region cancers; hodgkin's disease, lymphomas, acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). Side effects: neutropenia, leukopenia, thrombocytopenia, anemia; itching, nausea, edema and fatigue, heart failure (CHF), cardiomyopathy, heart Dysarrhythmia; Hair loss, loss of appetite, constipation, diarrhea, skin and nail bleaching; Dehydration, acute allergic reaction (anaphylaxis), convulsions, coma, conjunctivitis, general weakness, fever, weight gain. Photophobia, necrotic colitis, myelosuppression, hyperurameemia [10]. In case of radiation therapy, hyperpigmentation of Irradiated areas; Oro-pharyngeal ulcers, which makes difficulties in nutrition; Lips and tongue swelling [11, 12].

Etoposide
Etoposide is an anti-cancer agent that prevents the growth and spread of cancer cells in the body. Etoposide is used against lung cancer during the combined chemotherapy with other tumor medications.
Side effects: fever, flu symptoms, unusual bleeding (nose, mouth, vagina or rectum), petechiae on the skin; itching, dark urine, light stools, jaundice, convulsions; unexpected breast pain or discomfort, wheezing, dry cough; hair loss.
Loss of appetite, mouth and throat pain; nausea, vomiting, stomach pain; diarrhea, constipation; unusual or unpleasant taste in the mouth [13].

Mitoxantrone
Mitoxantrone is an anti-cancer agent that prevents cancer cells production and reduces their growth and metabolism Mitoxantrone also affects the immune system. It is used to treat certain types of prostate cancer and leukemia.

Side effects: Symptoms of infection such as fever, sore throat, flu symptoms, inadequately easily bleeding (nose, gums), or spontaneous bleedings, black, bloody stools; bloody stool or bloody vomiting; loss of appetite, unusual weakness; pain or feeling of burning, uneven heartbeat; swelling, rapid weight loss; difficult breathing. hair loss, menstrual bleeding; missed menstrual periods; rhinitis; feeling fatigue; depressive mood; diarrhea, constipation; pyrosis, stomach pains; nausea; oral ulcers [14, 15].

Doctetaxel

Doctetaxel is an anti-cancer agent that prevents the growth and metabolism of cancer cells in the body. It is used to treat breast cancer, lung, prostate, stomach cancers, and cancers of head-neck area.

Acceptance of the drug is contraindicated during pregnancy, liver diseases, and in case of presence previous chemotherapy in medical history; kidney disease; history of liver disease or alcoholism; heart disease, heart failure; fluid retention or swelling; allergy to any medication; The use of Doctetaxel may increase the development of other tumors, such as leukemia.

Side effects: Allergic reactions, neutropenia, edema, rapid weight loss, edema and redness on the extremities. weakness, sensation of burning, pain or tingling; confusion, drowsiness; signs of infection - fever, hepatomegaly, anemia, thrombocytopenia; spontaneous bleedings, petechiae; dark urine, light colored stools, jaundice; hair loss, muscle pain, stomach pain, loss of appetite, vomiting or diarrhea, pain in the mouth. Side effects in elderly and adolescents may have more sever manifestations [16].

Vinblastine

Vinblastine is a chemotherapeutic agent that is used for treatment of different types of cancer.

Common side effects (indicated in 10% of patients): infection risk, deterioration of vision; petechiae and bleeding; fatigue and weakness; loss of appetite, depression, headache, jaw pain, skin rash, heart dizziness, dizziness, high blood pressure [17].

Vendezin

Vendezine is a chemotherapeutic agent that is used for treatment of various types of cancer.

Common side effects: infection risk, deterioration of vision, spontaneous bleeding, fatigue and weakness, hair loss, deterioration of hearing, constipation, muscle weakness, rash, headache, dizziness, unpleasant taste in mouth, loss of appetite, jaw pain [18].

The main changes in the mouth cavity during chemotherapy

Patients with chronic dental problems and oral hygiene are an important risk group that may develop acute odontogenic infections on the background of immunosuppressive medications used in chemotherapy [23]. However, such complications are significantly lower than the mucous membrane reaction [24, 25].

Oncology centers provided the protocols, which can be used to manage odontogenic infections in oncologic patients. The protocols are outlined in tables (see Table 1; Table 2).

Table 1.
The empirical protocol of endodontic treatment in patients with myelosuppressive chemotherapy

Diagnosis	Management
Reversible pulpitis	Caries-control
Irreversible pulpitis	Initial biomechanical preparation of canal(s); temporary double closure
Necrotic pulp with chronic periapical pathosis	No endodontic treatment unless patient has 7 days from completion of endodontic therapy to onset of myelosuppression (<1,000 granulocytes/mm3)
Necrotic pulp with acute periapical pathosis	Endodontic therapy or extraction depending on systemic status of patient and scheduling of chemotherapy

Table 2.
Protocol for tooth extraction

1	Primary wound closure with multiple interrupted sutures
2	Ten days between extraction date and granulocyte count <500/mm3
3	Avoidance of intra-alveolar hemostatic packing agents
4	Platelet transfusion if platelet count <40,000/mm3
5	Prophylactic antibiotics if granulocyte count <2,000/mm3

It should be noted that since 1990, for more than 20 years, surveys and observations are on oncologic patients who have oral complications because of chemotherapy [26]. The literature contains caries, odontogenic infections, mucositis, oral mucous membrane problems.

The protocols that are provided by the institutions are mainly used for managing of adult patients. However, it is not accurate, preventive guidelines for managing oral cavity complications of pediatric patients. Also, there is no data about the dynamics of permanent dentition changes caused by chemotherapy in different age groups.

During the chemotherapy in pediatric patients the incidence of occlusion disorders is indicated in 55.6%. The agenesia - the qualitative damage to the teeth is mentioned in 20,4% according of the period of cancer diagnosis, the intensity of the chemotherapy and the age of the patient; microdontia – in 30,6%. These pathologies are related to the matches of teeth calcification period and the chemotherapy course [20].

Enamel hypoplasia and discoloration of permanent teeth are the most common defects among the results of chemotherapy conducted in early age [28]. Hypoplasia is the result of damage of ameloblasts function, because of chemotherapy their reproductive and sectarian functions are violated, also – calcium intake via their membrane. During the tooth calcification, the transfer of the Hertwig's area causes the dislocation of the pulpal cavity to the bifurcation. As a result of cytotoxic medications, it is also possible to develop roots agenesis, hipodontia [31].

Chemotherapy usually violates the function of the salivary gland. This violation is temporary and reversible. However, it causes discomfort, It affects speech and chewing function. The number and quality of saliva in patients is changed. Amylase and peroxidase increases, simultaneously are reduced IgA, and IgG. Because of these changes even mild trauma of oral mucous membrane can contribute the development of mucositis. The functions of saliva are reduced, such as lubrication, humidity, and antimicrobial activity [31].

It is also noticeable, that the saliva acidity changes are observed, especially – in the stimulated saliva. There are also changes in electrolytic substance (N + and K +), which is likely to be reduced the saliva flow from salivary glands. The amount of urea increases. All of the mentioned factors are supporting the growth of oral pathogenic microflora [31].

In the literature it is indicated, that after the completion of chemotherapy the salivary function will be restored in about 12 months [32].

The use of large amount of water, the use of sugar free chewing gums and candies can provide serious assistance to the patient to avoid hyposalivation and the effect of xerostomy during chemotherapy.

The damages according to chemotherapy in patients under the age of 5 years, include not only the present organs of the oral cavity, but also they are dangerous for the future occlusion. It is possible to develop pathologies such as pulp cavity expansion (based on delay in dentinogenesis process); tooth development interruption; chemotherapy leads to qualitative defects of teeth; the volume of defects depends on the type of medication and the management of oral cavity disorders [19].

Conclusion:

It is logical, to take in considering that with changes of the hard tissues of the tooth, pathogenic changes in bone tissue are also possible. From a single case it is possible to conclude that during the chemotherapy in pediatric patients, the resorption of the alveolar bone, osteoporosis, permanent teeth mineralization processes violation will be occurred.

Unfortunately, in the literature there is no accurate statistical data about these changes And it would be desirable to conduct surveys in this direction.შესაბამისად,

Due to the work of the pediatric dentists, the following issues remain on the agenda:

1. What is the frequency of the alveolar bone early onset during chemotherapy intervention?
2. Specifically, which chemotherapeutic medication is provoking alveolar bone early onse;
3. How to manage the premature bone set during chemotherapy;
4. How to protect the future permanent teeth from abnormal changes.

So, in our opinion, still under question remain very interesting and practical aspects, which require further research.

Recommendations of oral cavity caring in the process course of chemotherapy

From the above discussed information it can be concluded that almost all chemotherapeutic agents are characterized by oral cavity complications that can be avoided by the following preventive activities:

1. According to consensus of the National Institute of Health [19], dental examination and accompanying appointments to chemotherapy are essential for maintaining healthy oral cavity. So, for this purpose, 2-3 weeks before the start of the course of chemotherapy is necessary to book appointment with a dentist;
2. To control the dental plaque accumulation the patient is taken into the individual recommendations of the caring oral cavity. However, the care of the mouth is a very difficult process, taking into account the physiological-emotional status of the oncologic patient. Therefore, only dentist-patient communication is not enough. It is also necessary the involvement of clinicians, oncologists, dentists and patient's family members [20].
3. Regarding to avoid oral cavity complications caused by chemotherapy, it is recommended to reduce the epithelial velocity by using cryotherapy. For this aim it is recommended to use ice bricks for 30 minutes (sucking of the ice). This method reduces the formation of mucosits by about 50% in Fluorouracil chemotherapy [21].
4. To reduce stomatotoxicity it is also permissible to use Alopurinol mouthwashes. Antibacterial irrigations are also effective in patients with high risk of infection whose immune system is inhibited in chemotherapy [3].
5. To reduce the risk of mucosits development, the mouthwash with backer Soda solutions is provided. Or cleansing of oral cavity mucosa, with salt [22]. It should be noted, that sodium hypochlorite solution significantly reduces acidity of oral cavity. This factor promotes safety not only soft tissues of the oral cavity but also the protection of hard tissues.

6. In the literature also is included information about "Magic solution", effectiveness of this solution is quite high. It contains the following components: Diphenhydramine, viscous Lidokain, Bisimut subalicycilitis and corticosteroids, also Magnesium aluminum hydroxides, and Nistatin, syrup of sugar substitutes [3, 17].
7. While taking care of chemotherapy in children, it is also necessary to visit a dentist prior to treatment. Planning frequent visits during the course of chemotherapy for the management of xerostomy and its related problems (once in a 6 months or more) [22].

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