Oral Complications Due to Radiotherapy and Chemotherapy in Cancer Patients

Powikłania w jamie ustnej po radioterapii i chemioterapii u pacjentów leczonych onkologicznie

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Abstract

Chemotherapy and radiation therapy are the most common treatments used for the management of cancer patients. It can be used individually or together as adjuncts when a treatment protocol is planned. Unfortunately, in the process of treating one disease, the patient will have to endure the complications and side effects of the treatment. Chemotherapy has a systemic effect, whereas radiotherapy only affects the site of irradiation. The oral cavity is almost always affected, especially in head and neck cancer patients. Complications such as mucositis, dysgeusia, osteoradionecrosis, oral infections and dental developmental abnormalities are just to name a few. These side effects can greatly affect the quality of life of a patient either before, during or after cancer treatment. Hence, it is of up most importance that a clinician is well-versed with the possible complications and works towards helping the patient go through his treatment as comfortably and pain-free as possible.

Key words: chemotherapy, oral complications, radiation therapy, mucositis.

Słowa kluczowe: chemioterapia, radioterapia, powikłania w jamie ustnej, mucositis, popromienna martwica kości.

Sir Rupert Willis defined a neoplasm as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persists in the same excessive manner after the cessation of the stimuli which evoked the change. Neoplasms may be benign, pre-malignant or malignant. Malignant neoplasms are commonly known as cancer. Cancer cells divide rapidly and grow uncontrollably. Cancer has a tendency to destroy the surrounding normal tissue, it can metastasize to other organs through the bloodstream or lymphatic system and can eventually kill the host.

With the advancement of technology and the progression of research, many treatment options have been made available to eradicate cancer and extend the life span of cancer patients. Among which are surgery, chemotherapy, radiation therapy, immune therapy, hormonal therapy and gene therapy (still in the investigational stage) [1]. Unfortunately, management such as chemotherapy and radiation therapy lack selectivity. They act upon both tumour cells and normal cells [2].

The oral cavity is susceptible to the direct and indirect toxic effects of chemotherapy as well as the effects of radiotherapy in the region of irradiation. Susceptibility is due to factors such as [3]:

1) High cellular turnover rate of the oral mucosa,

2) Complex and diverse microflora of the oral cavity,

3) Oral tissue trauma occurring during normal oral function.

Hence, the patient undergoing treatment for one disease inevitably develops side effects and complications induced by chemotherapy and/or radiotherapy. It is important for the practitioner to know, anticipate and identify these complications so that he can treat the patient accordingly and possibly administer prophylactic measures.
Soft Tissue Complications

Mucositis

Oral mucositis is defined as the inflammation and ulceration of the oral mucosa with pseudomembrane formation; it is a potential source of infection which may lead to death [4]. 90–97% of patients receiving radiotherapy of the head and neck region develop a certain degree of mucositis as a common complication. Of these patients, who are receiving radiotherapy with or without chemotherapy, 34–43% develop severe mucositis [5]. Five to seven days following therapy, erythema followed by white plaques are seen, which are very painful when touched [6]. Due to pseudomembranes and ulceration, there is epithelial crusting and fibrin exudate. In a more severe form, there is exposure of underlying stromal connective tissue due to loss of epithelial cells [7]. Painful ulcers frequently result in dietary changes and the need for parenteral narcotics for relief. Ulcerated mucositis provides an entryway for systemic invasion by bacteria or their cell wall products [8]. It also affects the patient’s quality of life as it limits basic functions such as speech, mastication and swallowing of saliva.

Oral mucositis can be classified into 5 grades according to the World Health Organization (WHO) [9]:

Grade 0 – Absence of mucositis,
Grade 1 – Presence of painless ulcer, erythema or mild sensitivity,
Grade 2 – Presence of painful erythema or ulcers that do not interfere with the patient’s ability to take food,
Grade 3 – Confluent ulcerations that interfere with the patient’s ability to take solid food,
Grade 4 – Severe symptoms requiring enteral or parenteral support.

Factors that influence the frequency and severity of mucositis are:

- Type of tumour (haematological disease) [10],
- Age of patient (young patients) [10],
- Oral and dental health (poor oral hygiene) [11],
- Nutritional condition of a patient,
- Liver and kidney function,
- Type of cytotoxic drug [12],
- Frequency of administration of the drug (prolonged or repeated low-dose administration),
- Radiation dosage.

Salivary Gland Damage and Xerostomia

Radiation in the region of the salivary glands destroys the glands blood supply and the glandular tissue. Chemotherapy and radiotherapy have been shown to cause a significant decrease in salivary flow leading to xerostomia. Patients may feel dryness, burning sensation, discomfort, cracked lips, alterations in the tongue surface, and difficulty in wearing dentures as well as difficulty in speaking, swallowing and chewing. Furthermore, this leads to a rapid progression of dental caries, periodontal diseases and oral infection. Hyposalivation also favours the emergence of mucositis [2].

Dysgeusia

Dysgeusia is an impairment of sense of taste. It initially manifests a few weeks after starting chemotherapy or radiotherapy. The effects are usually reversible within a few weeks. Patients experience an unpleasant metallic taste during chemotherapy as a result of diffusion of the drugs into the oral cavity [13]. Bitterness is the most influenced by cancer and its treatment. Factors contributing to this taste alterations are damages to the taste buds, disrupted innervations and decreased salivary flow [14]. Dysgeusia may be related to the alterations in concentrations of sodium, potassium and calcium in the taste bud cell receptors [15].

Bleeding Tendencies

Thrombocytopenia as a consequence of bone marrow aplasia and/or liver toxicity resulting in an alteration of synthesis of coagulation factors to cause bleeding in the oral cavity. It is clinically presented as petechiae, ecchymosis, hematomas or diffuse bleeding [13]. It usually appears after trauma to the mucosa during chewing or in patients with pre-existing periodontal conditions.

Trismus

Patients who are suffering from tumours of the palate, nasopharynx and maxillary sinus are likely to develop trismus, shortly after radiation therapy begins. Management of this condition with exercise of the muscles involved and using bite openers are important as without it, eating and dental clinical procedures become a hefty task. Chronic trismus eventually progresses into fibrosis of the muscles [16].
Hard Tissue Complications

Developmental Disturbances

In children receiving chemotherapy, there has been delay in dental development, hypoplasia and microdontia. Chemotherapy has a systemic effect; as a result, developing odontogenic cells are susceptible to damage. On the other hand, radiotherapy only affects cells in the zone of irradiation [17].

The size and shape of the crowns of deciduous dentition is not affected as it is determined and formed before birth, whereas macrodontia is observed in permanent dentition due to the effects of drugs, such as vinblastine and vincristine acting upon mature odontoblasts and ameloblasts. In children below 5 years old, morphological anomalies of roots of upper and lower premolars are seen. However, alterations of the roots of upper and lower canines, premolars and molars are seen in older children. Chemotherapeutic drugs act upon the microtubules of odontoblasts resulting in interruption of the formation of collagen fibrils and dentinal matrix, producing thin and sharp pointed roots [18]. Irradiation can also induce disturbances in odontogenesis such as microdontia, short or blunted roots, small crowns, malocclusion, incomplete calcification, taurodontism, premature closure of apices and also delayed or arrested development of teeth [19].

Dental Caries

Chemotherapy and irradiated patients have been found to have a higher incidence of dental caries [3]. Generally, this is due to decreased salivary flow, decreased pH, reduced buffering capacity, increased viscosity and increased colonization with *Lactobacillus* spp. and *Streptococcus mutans*. Radiation caries are most commonly seen as superficial lesions on enamel surface, but circumferential caries attacking the root cementum and dentin resulting in the breakage of the crown is also common [21].

Bone Complications

Osteoradionecrosis

Osteoradionecrosis is the most severe complication of radiation, as it lacks curative treatment and its ill effects on oral functions, appearance and psychosocial problems associated with the disease [22]. Osteoradionecrosis can be defined as radiological evidence of bone necrosis within the radiation field, where tumour recurrence has been excluded [22]. The mandible is most prone to osteoradionecrosis because of its poor vascularity and high bone density. The bone becomes hypovascular, hypocellular and hypoxic. Factors contributing to this disease are [23]:

- Trauma,
- Type of radiation,
- Dosage of radiation,
- Volume of tissue involved,
- Presence of teeth (twice as high in dentate patients),
- Poor oral hygiene,
- Alcohol and tobacco use.

Osteoradionecrosis has a wide range of clinical presentations ranging from small stable asymptomatic region of exposed bone to full scale osteoradionecrosis that is accompanied with severe pain, foul smelling necrotic bone of green-grey colour and suppuration [24].

Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ)

Bisphosphonates are used for the management of breast cancer, prostate cancer, multiple myeloma and other non-malignant diseases, such as osteoporosis and Paget’s disease [25]. BRONJ is a pathology resulting in a non-healing, necrotic sequestrate of bone in patients on bisphosphonate therapy [26]. The disease usually only makes itself visible following triggering events such as dental extractions and soft tissue trauma. Also, it is usually present long before clinical signs and symptoms are noticed [27, 28]. Clinically, it is characterized by progressive and sustained pain, which sometimes may require analgesics to control the symptom [29]. Patients undergoing bisphosphonate therapy require thorough dental examination, failure of which may have an undesirable outcome. It is often noted that even an elective procedure like tooth extraction in patients on bisphosphonates can result in unhealed extraction sockets and ulcerations of overlying epithelium. There will be
multiple exposed sites of bony spicules with occasional purulent exudate [26].

Staging classification for osteonecrosis of the jaws by bisphosphonates [29]:

Stage 1 – Exposed bone necrosis or small oral ulceration without exposed bone necrosis, but without symptoms,

Stage 2A – Exposed bone necrosis or a small oral fistula without exposed bone necrosis, but with symptoms controlled with medical treatment,

Stage 2B – Exposed bone necrosis or a small oral fistula without exposed bone necrosis, but with symptoms not controlled with medical treatment,

Stage 3 – Jaw fractures, skin fistula, osteolysis extending to the inferior border.

Infections

Chemotherapeutic drugs and radiation both affect the bone marrow, thereby resulting in anaemia, leukopenia and thrombocytopenia. The greater the degree of neutropenia, the higher the
risk of infections, which is the highest when the granulocyte count drops below 0.5 G/L. As for anaemia and thrombocytopenia, it has an indirect effect on incidence and severity of infections. Consequently, the oral cavity becomes more susceptible to infections.

**Bacterial Infections**

Saprophytic bacteria become more aggressive as granulocytes decrease and fragility of oral mucosa is increased. *Streptococcus viridans*, *Prevotella* spp., *Fusobacterium* spp., *Aggregatibacter actinomycetemcomitans* and *Actinomyces* spp. are associated with oral cavity infections [30]. Manifestations are locally on the gingiva, mucosa and teeth. Necrotizing gingivitis is most commonly encountered.

**Fungal Infections**

Most common fungal infections are by *Candida albicans*, mainly due to bone marrow suppression, salivary alterations and mucosal lesions [31]. It commonly starts off as pseudomembranous candidiasis followed by erythematous candidiasis and angular cheilitis [13]. This infection can give rise to sepsis and lead to fatality if not adequately diagnosed, especially when caused by *Candida tropicalis* which a non-*Candida albicans* species. Clinically candidal lesions can be removed easily by scraping the surface of the mucosa [30].

**Viral Infections**

Viral infections are usually the result of reactivation of a latent virus such as herpes simplex virus (HSV), varicella-zoster virus (VZV) and Epstein-Barr virus (EBV), whereas cytomegalovirus can result from both reactivation of a latent virus or a recently acquired virus [32].

HSV lesion severity increases drastically with greater immune suppression. Lesions are more diffuse but less painful in chemotherapy patients compared to patients undergoing radiotherapy. Recurrent intraoral HSV infection may also present ulceration in mucosal areas, which have not adhered to the periosteum, such as the tongue and soft palate [32].

VZV lesions may involve several dermatomes in immunocompromised patients or may have a more generalized distribution. Patients may experience a series of non-specific prodromic symptoms followed by vesicular eruptions along a dermatome. Pain is constant and described as burning. Manifestation is usually several weeks after termination of chemotherapy. CMV is characterized by multiple mild or moderate ulcerations with irregular margins and a granulomatous base covered by a fibrin exudate [13].

**Neurotoxicity**

Chemotherapeutic agents, such as vincristine and vinblastine, have the ability to cause direct neurotoxicity. Comparatively, vinblastine is less neurotoxic than vincristine. One week after terminating chemotherapy, patients may feel deep and pulsating mandibular pain, usually in the molar region. It is very important to distinguish this pain from pain of pulpal origin such as pulpitis. In a handful of cases, weeks, even months after completion of chemotherapy, patients may have dental hypersensitivity [13].

The complication of chemotherapy and radiotherapy should be well considered by the clinician to minimize oral morbidity before, during and after cancer treatment as well as throughout the lifetime if the patient.

**References**


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