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Oral Complications Related to Cancer Therapies in Children

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ABSTRACT

Background: While early diagnosis and advances in the cancer therapy for children continue to improve resulting in higher survival rate, oral complications remain a significant cause of morbidity and potential mortality [1-5]. Cancer therapy-related oral complications are common consequences in pediatric patients undergoing chemotherapy, myeloablative chemotherapy prior hematopoietic stem cells transplantations, or radiation therapy for head and neck cancers or solid tumors. Children and adolescents present acute and long-term oral side effects more than adults with incidence about 30-100 %.

Methods: To investigate acute and long term oral side effects of cancer treatment in children, a literature research (PUBMED, EMBASE) as been leaded; research inclusion criteria were: reviews or scientific papers about children (0-18 years old) and cancer therapy published from 2000s to nowadays.

Results: Mucositis, oral infections, taste dysfunction, xerostomia and bleeding are recognized as common acute sequelae with risks for severe pain, malnutrition, potential source of systemic infections resulting in increased hospitalization and higher costs of care.

Furthermore, several dental and skeletal developmental abnormalities are well documented in pediatric cancer patients long-term survivors, and in allogeneic transplant children healing can take longer specially in instances where oral acute or chronic GvHD occurs.

Conclusion: Since oral complications can occur at all stages of cancer therapy and they can significant interfere with good prognosis, it should be mandatory to detect, treat and prevent them, in order to improve children's quality of life

Keywords: Cancer-childhood-sequelae-treatment

INTRODUCTION

Childhood cancers are a small proportion of the total number of cancer cases worldwide accounting for about 2% of the total number registered. Cancers occurring before the age of 15 are considered pediatric, but recently most centers treat children until they are 18 years old. The most common cause of the death from disease in childhood is cancer with an incidence of a new case every 150.000 inhabitants. The most frequent neoplasms are acute leukemia, lymphocytic and non lymphocytic, Hodgkin's diseases, non–Hodgkin's lymphoma, CNS tumors, neuroblastoma, retinoblastoma, Wilm's tumor and bone sarcomas [1-5].

Significant advances have been achieved in the treatment of all pediatric cancer patients as concern survival. For most patients the first clinical results have been obtained in the early 1970s thanks to the coordinated effort to treat cancer with a more aggressive, multimodality approach. The best results have been achieved in children affected by lymphocytic leukemia, lymphomas and soft tissues sarcomas [1-5].

Since 1960s it was clear that administering anticancer agents in combinations was the only effective treatment in childhood cancers. In acute lymphoblastic leukemia (ALL), for example, the use of combined chemotherapy, as compared with single drug regimens, increased the remission rate and the duration of remission. As concerns antitumor chemotherapy, a requisite could be the specificity for the target, to eliminate the neoplastic cells not affecting the others. This ideal prerequisite is uneven since the vast majority of molecules are not capable to act against exclusively cancer cells. In fact most agents do not have a selective effect on tumor cells and interact with all cells of the organisms. In fact the dosage of drug is critical for its therapeutic effect. Nevertheless if a drug it is not used at the correct dosages can prone the patient to infections or severe mucositis due to local toxicity and neutropenia [1-5].

As concerns radiotherapy, ionizing radiation delivered in doses induces unavoidable changes in the surrounding and adjacent normal tissue, causing compromises in function and host defenses and severe complications. The degree of these changes is directly proportional to the volume of

tissue irradiated and the total dose given and is inversely proportional to the number of fractions and total time in which this dose is delivered. These radiation changes are the direct result of the killing of normal tissue cells as expressed at the tissue level. It is this radiation damage to normal cells that determines the limiting factor in maximal treatment of many cancers.

While early diagnosis and advances in the cancer therapy for children continue to improve resulting in higher survival rate, oral complications remain a significant cause of morbidity and potential mortality [1-5]. Cancer therapy-related oral complications are common consequences in pediatric patients undergoing chemotherapy, myeloablative chemotherapy prior hematopoietic stem cells transplantations, or radiation therapy for head and neck cancers or solid tumors. Children and adolescents present acute and long-term oral side effects more than adults with incidence about 30-100 %. Since oral complications can occur at all stages of cancer therapy and they can significant interfere with good prognosis, it should be mandatory to detect, treat and prevent them, in order to improve children's quality of life [1-5].

MATERIALS AND METHODS

To investigate acute and long term oral side effects of cancer treatment in children, a literature research (PUBMED, EMBASE) as been leaded; research inclusion criteria were: reviews or scientific papers about children (0-18 years old) and cancer therapy published from 2000s to nowadays.

RESULTS

Mucositis, oral infections, taste dysfunction, xerostomia and bleeding are recognized as common acute sequelae with risks for severe pain, malnutrition, potential source of systemic infections resulting in increased hospitalization and higher costs of care.

Furthermore, several dental and skeletal developmental abnormalities are well documented in pediatric cancer patients long-term survivors, and in allogeneic transplant children healing can take longer specially in instances where oral acute or chronic GvHD occurs [1,6].

Acute Complications

Oral Mucositis

Oral mucositis is one of the most debilitating complications in children receiving cancer therapy. Cancer therapy–induced mucositis occurs in 40-80% of children and it is higher in patients undergoing myeloablative chemotherapy prior HSCT and/or simultaneous radiotherapy.

In children and adolescents, the risk of mucositis is higher compared with adults probably due to the high incidence of hematological malignancies, more intensive and aggressive cancer protocols and higher mitotic index of epithelial basal cells. Despite this, the mucositis in pediatric patients tend to resolve more quickly [6-8].

Pathogenesis of mucositis results from a physiopathologic process involving rapidly dividing epithelial basal cells, started from chemo-radiation therapy induced damage. Several risk factors related to host status can influence the development and severity of mucositis such as: age, female gender, poor nutritional status, type of malignancy, drug-induced xerostomia, previous mouth damage, poor oral hygiene and genetic predisposition. In addition, cancer treatment-related factors are also associated with an increased risk of mucositis [7,8].

Use of chemotherapeutic agents is particularly stomatotoxic and the drug-induced mucositis is related to their dosage and schedule. Finally, radiotherapy-related risk factors depend on dose, fractioning and site of radiotherapy, radiation combined with chemotherapy and conditioning regimens in HSCT recipients.

Oral mucositis becomes clinically evident at 4-5 days following chemotherapy infusion and generally peaks at 7-14 days after. Uncomplicated mucositis resolves spontaneously within 3 weeks after chemotherapy is ended. Often mucositis is not limited to that period but it may develop into a longer lasting pathology with devastating effects on the patient's recovery and hampering complete well being for years.

Radiation-induced mucositis develops later; it starts at a cumulative dose of 10Gy, peaks at 30Gy of radiations dose and requires 3 to 6 weeks after the completion of radiotherapy for healing of oral tissues. Chronic mucositis occurs rarely after radiotherapy.

Children undergoing cancer therapy describe (when it is possible) an initial burning or tingling sensation followed by intolerance to food.

In chemotherapy-related mucositis the clinical early sign is erythema: although it can occur in any region of the mouth, is frequently localised on non-keratinized areas such as the inner surfaces of the cheeks and lips, soft palate, lateral and bottom surface of the tongue and the floor of the mouth.

In contrast, radiation-induced mucositis involve the tissues limited to the exposed field, including hard palate and gingiva, and it begins to manifest at cumulative radiations dose about 10Gy, with erythema or mucosal white discoloration due to transient hyperkeratinisation.

Ulcerative lesions occur at 7-14 days after chemotherapy or at cumulative radiations dose of 30-50Gy [9,10]. Mucosa ulcerative breakdown is always a potential focus for localized infections that, especially in the neutropenic child, offer an easy access to the bloodstream for the oral flora and allow disseminating life-threatening infections.

Pain associated with ulcerative mucositis can inhibit patients from eating, swallowing, drinking, and requires analgesic management with topical anaesthetics followed with non-steroid anti-inflammatory agents. Supportive parenteral nutrition, consequently longer hospitalization and additional hospital charges are more commonly required with lower quality of life [3-10].

Ulcers, pseudo membranes and pain cause droll in children who cannot swallow normally. In addition, severe mucositis often compromises the care rates and can result in interruption or modification of anticancer treatment planning, as dose reduction and/or treatment discontinuous are necessary in order to heal oral lesions in children.

Mucositis can not only prevent the oral intake of food and liquid, but it can also lead to oropharyngeal airway embarrassment secondary to swelling, bleeding and a decreased ability to protect the airway.

Life-threatening infections, total parenteral nutrition, days of fever, antibiotic and narcotic analgesic use, 100-day mortality and higher cost of care are clearly related to the severity of mucositis in childhood.

There are multiple scoring methods to grade mucositis. Objective, subjective, and a combination of both findings have been used to measure the severity of mucositis [1-8].

The two commonly used scoring tools for assessing oral mucositis in routine oncology management are the WHO scale, that combines both objective mucosal changes (redness and ulceration) and functional outcomes (ability to eat) and the NCI Common Toxicity Criteria (NCI CTC) for mucositis, which have been developed for patients receiving radiation therapy, chemotherapy, and conditioning regimens for HSCT.

These scales are graded from 0-4 describing the progression of mucositis from mild to moderate, to severe and life threatening. Other valid scales have also been developed, such as the Oral Mucositis Assessment Scale (OMAS), the oral mucositis index (OMI) and OAG, Walsh scale, although they are mainly purposed for research applications in adults. A major limitation to mucositis assessment in paediatric patients is the lack of an accepted, validated and objective scoring system for mucositis in this population. In addition, many limiting factors characterize the oral assessments; the children are often uncooperative and the smaller oral cavities limit the examination and a difficult clinic approach with inadequate illumination and an unfavourable time factor may increase the detection of changes in their oral cavity. Since the ability to measure mucositis is fundamental for clinical trials for mucositis prevention and treatment, consequently, a multi-disciplinary and multi-national group of investigators developed the Children's International Mucositis Evaluation Scale (ChIMES), specific for use in children with cancer. ChIMES scale is available both in an electronic format and in a paper format [11,12].

Furthermore, a lot of age-related inabilities to explain and describe subjective symptoms require careful exams and an expert and suitable team of investigators. In the absence of effective measures for preventing oral mucositis, its management in children is mostly palliative and focuses primarily on reduction of factors that will increase injury and irritation of the oral mucosa, in limiting hospital stays and costs of care, and in improving quality of life. Good oral hygiene protocols should be applied during and after chemo-radio therapy motivating the children and their caregivers to maintain an appropriate level of oral hygiene in order to minimize the risk to

develop decay, local infections, haemorrhage and oral mucositis. Preventive oral protocols are based on assessment, patients' education, and oral care with a multidisciplinary collaborative team approach.

Late strategies for preventing and treating cancer therapy–related oral mucositis in children suggest oral cryotherapy for patients receiving fluorouracil (5-FU) or an other short serum half-life chemotherapeutic agents because of the intake of ice reduces the absorption of mucotoxic agents through local vasoconstriction. Experts recommend that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to prevent oral mucositis [6].

In the last years, phototherapy as been proposed to prevent and treated cancer therapy related oral mucositis: low level laser therapy at a wavelength of about 632 nm, power of 40mW energy density of $2J/cm^2$ for preventive use and 5J/cm2 for therapeutic effect has been demonstrated to be effective in children undergoing chemotherapy or HSCT [7,10,13-16].

In addition, morphine 2% mouthwashes and doxepin 0.5% mouthwashes may be effective to treat pain due to oral mucositis.

Benzydamine oral rinses with cytoprotective, anesthetic and antimicrobial properties, cytokines and hematopoietic-growth factors promoting a rapid re-epithelialisation, systemic zinc supplement are suggested. The use of topical anesthetics, recommended for pain, should be supervised in children, to avoid the risk of swallowing with consequently loss of gag reflex [6].

Like in adults, chlorhexidine is not recommended in childhood mucositis because of its characteristic side effects (significant stinging, burning and dysgeusia) which cause mouth discomfort and reduce patient compliance [6].

Oral infections

- With the complete ablation of the immune system and compromise of mucosal barriers, children are at risk for all types of oral infections.Viral – Herpes group viruses (*HSV, CMV*); Adenovirus
- Fungal – *Candida, Aspergillus, Mucormycosis*
- Bacterial – Gram + oral flora (*Streptococcus* spp., *Staphilococcus* spp.) and opportunistic and acquired Gram - organisms (e.g., *E. coli, Enterobacter, Pseudomonas, Neisseria, Klebsiella, Serratia, Fusobacterium*)

Bacterial infections most commonly involve gingival tissues, though any mucosal surface is potentially at risk. Oral mucosal infections may cause fevers and can result in systemic bacteremia. Chlorhexidine mouthwash is usually recommended in combination with good oral hygiene.

A specialist in infectious diseases is usually involved when treatment protocols are drawn up. Secondary infection and bleeding can also be associated with exfoliation of primary teeth and eruption of permanent teeth. Treatment of documented oral infection is directed by the result of

laboratory test for antibiotic sensitivity. A combination of topical and systemic antibiotic can be used if bacteria demonstrate sensitivity to the chosen drug.

HSV causes most of the oral infections in cancer children. The clinical features of HSV oral infection are oral and extra oral ulcers with erythema and crusts. Often, oral ulcers can be confused with recurrent aphthous stomatitis or traumatic lesions; consequently, it's always important suspect it, in particular in the primary infection. It is not unusual to see the sudden emergence of herpetic stomatitis in cancer children and it is consequently important to be vigilant and alert to the possibility of these infections.

Because HVS infection is often a reactivation of the virus in previously infected children, oral or intravenous acyclovir, or more recently oral valacyclovir, is used prophylactically to prevent HSV reactivation in seropositive patients. Intravenous acyclovir is utilized to treat documented infection.

Oral **fungal** infections often develop in children undergoing chemo-radio therapy, especially during severe immunosuppression and neutropenia.

Prevention of fungal colonization and control of local infection may be of critical importance in avoiding systemic candidiasis.

Systemic antifungal prophylaxis protocols routinely use systemic azoles, especially fluconazole, with or without additional topical agents for documented oral infection. Despite Nystatine (mouthwash), miconazole (gel), clotrimazole (troches) or amphotericin B (mouthwash) are generally used to treat superficial oral Candida infections, Nystatine cannot be recommended for prophylaxis or systemic treatment, because it is not absorbed through the gastrointestinal tract. However, a combined topical/ systemic approach is definitely warranted to reduce the risk of systemic spread of infection. Invasive *Candida* and filamentous fungi (*Aspergillus, Mucormycosis*, etc.) are treated with aggressive systemic antifungal and surgical resection.

The use of prophylactic infectious disease protocols to prevent bacterial, fungal and viral infections has increased the frequency and severity of oral infections. However, when infection does occur, it is important to utilize careful laboratory diagnostic techniques to identify causative organisms and to monitor symptoms closely, because of the atypical presentations of oral infections in the phase of immunosuppression [17-20].

Salivary glands dinsfunction

Salivary glands dysfunction is related to toxicity from conditioning regimens prior HSCT and during chemo-radio therapy. The clinical features include parotitis, viscous saliva, hyposalivation and xerostomia. In pediatric patients, xerostomia remains the most involved dysfunction, because of the importance of saliva in maintaining oral health. Oral dryness worsens the quality of life causing changes in taste and difficulty in chewing, swallowing and speaking. Chemotherapy-induced xerostomia is transient and self-limitating, usually resolving in 48 hours.

Despite the damage caused by radiation is often irreversible and affecting the acini of the salivary glands, some patients nevertheless improve their salivary function by 2- 12 months after therapy ended. When the radiation beam directly involves parotids glands, xerostomia and hyposalivation are persistent. In pediatric patients decreased salivary flow leads to modified oral bacteria favoring caries-related microflora (*Streptococcus mutans, Lactobacillus*) and opportunistic infections, especially during periods of neutropenia.

Management of xerostomia remains primarily symptomatic. Salivary flow can be stimulated by sucking or chewing a sugar-free gum, in addition to artificial saliva or simply frequent rinses with fresh water. Sialogogues can be effective in preventing and treating xerostomia. Oral lubricants such as bicarbonate mouthwashes, and use of salivary substitutes can also be effective. To moist dry lips, lipsticks or lanolin creams and ointments may be helpful.

In order to reduce the risk of dental decay in children with xerostomia intensive oral care, frequent topical fluoride applications, sugar-free diet and fissure sealants can be suggested. In addition, the high risk of oral candidiasis needs antifungal therapy when indicated by documented overgrowth and /or infection [21,22].

Taste dysfunction

Cancer therapy is a frequent cause of loss of taste discrimination or altered sense of taste: sweet, sour, bitter and salty are affected. These sequelae may cause serious discomfort to the patients, reducing nutritional supply and interfering with physiological growth and weight. Children usually recover their sense of taste between 1 and 3 months after cancer therapy ended [23].

Furthermore several food-related problems are common in children undergoing antineoplastic therapy, due to mucositis, nausea and inappetence, with consequent lower food intakes. Therefore, prevention and management of childhood malnutrition are of primary importance [24-26].

Current protocols focus on improving smell and eye appeal of food and acceptable texture. It's recommended choosing foods typically preferred by children and adolescents (snacks and liquid nutritional supplements) when easily available. Zinc supplements have been reported to be effective in helping the recovery of the sense of taste, following head and neck radiation [27].

Oral haemorrhage

Oral bleeding ranges from 6% to 42 % in children undergoing cancer therapy and can vary between minor gingival oozing and frank bleeding. The most common risk factors are thrombocytopenia, coagulopathies, mucosal infections, trauma (especially on tongue and lips), mobile primary teeth, orthodontic appliances and poor oral hygiene. With severe thrombocytopenia in the presence of mucosal breakdown or infection, oral bleeding can be clinically problematic. When platelet counts above 20000/mm^3 can be maintained, the incidence and severity of oral bleeding are decreased and spontaneous bleeding is rare at 50.000/mm^3.

Oral bleeding is initially managed with direct pressure packs. Subsequently, topical haemostatic agents (thrombin, collagen clot-forming agents, etc), tranexanic acid as mouthwashes, topical vasoconstrictors (epinephrine or ice chips) can be used alone or in combination. More severe or persistent bleeding requires systemic therapy including administration of platelets or antifibrinolytic agents and dental cares [1].

Long Term Complications

Dental developmental abnormalities

Dental anomalies such as microdontia, hypodontia, enamel hypoplasia, over-retention of primary teeth, enlarged pulp chamber and delayed or arrested root development, root stunting and agenesis are well known long-term effects of antineoplastic therapy in survivors of childhood cancer. Chemo-radiotherapy administered during odontogenesis might affect developing teeth with consequently dental anomalies.

These sequelae may be related to the child's age at the beginning of cancer therapy (the risk of dental development alteration increases when cancer therapy starts before 5 years), the stage of tooth development, the type, intensity and frequency of treatment protocols used.

Children who underwent cancer therapy with mixed dentition have a higher incidence of dental anomalies, probably due to the effect of therapeutic damage on rapid odontogenic changes during this period.

Dental abnormalities caused by radiation are limited to the irradiated area; high-dose radiation during very early phases of tooth development may destroy the cells of the tooth germ and can lead to complete dental agenesis. In contrast, less drastic complications like microdontia, enamel hypoplasia and defective calcification and stunted or tapering roots occur with a lower dose or when radiotherapy starts at a later stage of dental development. Roots defects result when crown formation has completed.

Radiotherapy-related damages occur simultaneously in the bone, periodontal ligament and pulp. Whereas radiation damages cells only in the path of its beam, chemotherapy provokes systemic effects, interfering with the cell cycle and with intracellular metabolism of rapidly dividing cells in the whole body [28-30].

Developing odontogenic cells may be susceptible to chemotherapy damages causing disturbances in dental development as crown hypoplasia, microdontia, enlarged pulp chamber ,and root anomalies (conical roots and short V-shaped) mostly of the lower incisors and premolars.

Short half-life of chemotherapeutic agents causes usually localized dental defects, while complete dental agenesis is rare and it may result when repetitive and intensive chemotherapy is used.

In children undergoing chemo-radio therapy eruption of teeth can be delayed and the frequency of impacted maxillary canines appears to be increased.

With shortened root length alveolar processes can be consequently shortened, leading to decreased vertical dimension of the mandible and the lower third of the face.

Additionally, damage to jaw growth centres by conditioning regimens can lead to decreased size and mobility of jawbones, and their extent can be appreciated by a cephalometric analysis.

Cancer therapy may be associated with an increase of enamel hypoplasia and white spot lesions caused by interferences with ameloblasts during dental crown formation [31-34].

Dental Caries

Children during cancer treatment are at high risk of dental caries resulting from multiple factors. The damage caused by chemotherapeutic agents and radiation on salivary glands reduce the salivary flow and cause oral environment changes favouring caries-related microflora.

Furthermore the mouth dryness, due to the hyposalivation, often requires the intake of sugar-containing soft drinks contributing to increase the arising of caries. In addition, oral sucrose-rich pediatric medications (syrups) are common risk factors for dental caries.

Cancer therapy- induced enamel defects (white spots, hypomimeralization) increase the risk of dental caries especially in children treated in early years of their lives (3-5 years). In survivors, severe radiation tooth damages rapidly develop into decay.

During nausea and vomiting, acids coming from the stomach increase the risk of developing decay and children must rinse the mouth with water after each emesis episode. Finally, poor oral hygiene, carbohydrate-rich diet, long hospitalisation and psychological factors are well-known cause of predisposition for dental decay [34-37].

Trismus

Fibrosis of the masticator muscles due to high doses of radiation to the head and neck may lead to developing of trismus. In order to prevent and ameliorate this condition, daily stretching oral exercises and physical therapy during and after radiation (3 to 6 months) are recommended [1].

ORAL GvHD

While the frequency of GvHD is usually lower in pediatric patients than in adult population who underwent HSCT , the oral cavity can be involved with both acute and chronic forms of the disease. Oral GvHD usually presents as part of multi-system involvement, but in numerous patients it is the first or only manifestation of disease. Clinically the most common presentation is a combination of mucosal erythema, atrophy, and lichenoid changes appearing as hyperkeratotic striae, papules, and plaque. The oral manifestations of acute (30 days after HSCT) and chronic

(100 days post-HSCT) GvHD are extremely similar, characterized by pseudomembranous ulcerative lesions. In addition to oral mucosal lesions, GvHD affects salivary glands and can cause xerostomia. Mucoceles also result from mucosal and ductal damage to minor salivary glands by lymphocytes.

Patients with oral GvHD must carry out careful and effective oral hygiene. Oral GvHD is best managed with successful systemic therapy. The primary goal of topical therapy for oral GvHD is to reduce symptoms. Topical oral steroids (rinses, creams or gels) can be applied to help resolve ulcers as well as to help reduce symptoms (burning, sensitivity, etc.) and can reduce mucosal inflammation and mucocele. Topical cyclosporine in rinses or mucoadherent gels has been reported to help oral GvHD [2,38].

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