

Orthodontic strategies in pediatric oncology

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ABSTRACT

Cancer in children is not uncommon and can occur at any age. After summarizing the pediatric cancer epidemiology, dentofacial orthopedics and orthodontics during anticancer treatments will be discussed. Orthodontic management in children with cancer differ depending on the type and time of the anticancer therapy: before, during and after chemo- or radiotherapy. The pathophysiological, psychological, administrative and technical concerns are described for every situation. Finally, we suggest some recommendations, according to the current knowledge and our own dentist experience in the pediatric oncology department of Rennes.

KEY WORDS

Hematologic neoplasms, cancer, anticancer agents, mucositis, orthodontics, child, adolescent

INTRODUCTION

The occurrence of cancer in children and adolescents is not uncommon. Effective patient support systems coupled with the prevention of complications have played important roles in improving survival rates and limiting long-term relapses. However, the orthodontic care of young people who have undergone or who are currently undergoing therapy remains a challenge for patients, their family members, and their orthodontists.

In this article, we first present a summary of the epidemiology of pediatric cancers

and a description of clinical situations that facilitate our discussion of strategic orthodontic treatments of patients. Then, we illustrate why ongoing orthodontic treatment is not desirable during cancer therapy, and we also mention “urgent” cases that may require the placement of orthodontic devices. We give our perspective on removable devices and on restraints. We end with cases of children in remission and who require orthodontic treatment. We detail the physiopathological, sociopsychological, administrative, and technical elements

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to be considered during the orthodontic evaluation of children afflicted with cancer. The incidence of facial bone tumors that can only be treated by maxillofacial surgery is uncommon and is therefore not addressed here.

The literature available on the orthodontic care of cancer patients is poor. The orthodontic management of patients after their cancer (which requires expertise and clinical experience) is still poorly defined by professionals. An American study

conducted via an online questionnaire among 4,800 American orthodontists (of whom 381 responded) has recently shown that even though most orthodontists claim to have treated patients cured of their cancer, none have treated more than 10 of them. In the absence of *evidence-based medicine* and official recommendations, our remarks are based on our experience as dental surgeons in the Department of Pediatric Hematology–Oncology of CHU Rennes.

THE EPIDEMIOLOGY OF PEDIATRIC CANCERS

Cancers vary according to age

In metropolitan France, every year, approximately 1,700 children under the age of 15 years and 800 adolescents between the ages of 15 and 19 years are diagnosed with cancer. Combining this information, the incidence is stable and the survival rate at 5 years of age was as high as 83% in 2011.

Pediatric cancers are of varied histopathological natures. In children under 5 years of age, tumors formed in the embryonic tissue are predominant, these variants include neuroblastomas, nephroblastomas, and retinoblastomas. At ages when orthodontic treatment should start, i.e., between 5 and 14 years of age, other cancers predominate such as leukemias (26%), central nervous system tumors (27.8%), and lymphomas (17%). The leukemias present in children are mainly acute leukemias. Overall 80% of them are lymphoblastic and less than 20% are myeloblastic, though the latter have less favorable prognoses. Malignant bone

tumors, including osteosarcomas and Ewing's sarcomas, have become more frequent during adolescence and represent 7.9% of cancers. Finally, Hodgkin lymphomas (22%), leukemias (12%), and thyroid cancers (9%)⁹ are mostly found from 15 to 19 years of age.

Multimodal therapeutic strategies

If young age is a risk factor for dental and orthodontic complications⁴, such complications are mainly related to the cytotoxic therapeutics used and the tumor location.

The protocols of multimodal therapies in children have serious ENT-related consequences, either because the tumor is the direct target (when the face is affected) or by the systematic involvement of the mucous membranes and thus of the buccal mucosa. The risks of immunosuppression, infection, and thrombocytopenia in certain phases of treatment limit the possibilities of orthodontic treatment.

It is therefore important to become aware of traditional, current, and future

treatment phases during the orthodontic care of young patients are affected, in remission, or cured of cancer.

Similar to lymphomas, for leukemias, treatments rely mainly on corticosteroids and chemotherapy. Some malignant hemopathies require hematopoietic stem cell transplantation (HSCT) with a dispensation that includes chemotherapy and sometimes total body irradiation followed by immunosuppressant treatment. The drug most often used is ciclosporin whose secondary gingival hypertrophy is a well-known side effect. One of the complications of allografting is the graft-versus-host reaction, which can reach the mucous membranes and requires enhanced immunosuppressive therapy with the addition of corticosteroids in most cases.

The use of radiotherapy is largely limited in the field of pediatrics because of its consequences on growth and development in general as well as the risk of secondary cancer, particularly in irradiated areas. However, it remains necessary for many brain tumors are treated by surgery and chemotherapy.

In conclusion, for some metastatic solid tumors, standard chemotherapy is supplemented by intensive chemotherapy requiring reinjection of patients' stem cells (autografting). Autografting is followed by craniospinal irradiation with an additional risk of thrombocytopenia and immunosuppression (as is the case with high-risk medulloblastomas).

Steps involved in systematic treatment and evaluation

The modes of discovery or relapse of cancer in children are variable. A change in the general state, an infectious

syndrome, or a hemorrhagic or tumor syndrome is a typical symptom of malignant hemopathies. Pain and MASS syndrome are the main signs of solid tumors. Both orthodontists and dentists should be alerted by signs suggestive of cancer such as a mucous mass, bone deformation, bone pain, and petechiae.

While diagnosing, an assessment of the spread of the disease and an exploration of the infected site are done before the start of any cancer treatment. This treatment is initiated at a pediatric oncology referral center. A personalized care plan is established, often involving a local network of professional teams and general hospitals. Depending on the areas, referral documents created within one network (oral health advice, specific diets, or drug contraindications) are shared with parents.

Patient care is punctuated by treatments administered during full hospitalization or in day hospitals. Between treatments, during a period known as the intertreatment interval, complications are monitored from home. Aplasia and mucositis sometimes occur with a fairly precise delay. There is a limited time frame during which dental care is possible: between the end of aplasia and the next course of chemotherapy. This time is too short for orthodontic care but still provides the possibility for assessment and urgent treatment with a minimum risk of infection.

The clinical re-evaluation of infection sources, mucosal conditions, and nutritional status is systematically performed between each cure and at each new treatment stage. Specific recommendations are made when patients are included in a research protocol.

Before HSCT, a more thorough infectious assessment involving the ENT

and bucco-dental spheres, is also performed. Before cervical or orofacial radiotherapy, a dental checkup is necessary because of the risks involved.

After the last therapeutic phase, an end-of-treatment assessment is performed. After complete remission, regular monitoring is continued for several years before it can be considered "cured." The involvement of dentists and/or orthodontists may be

required at each step. Thus, in all cases, before any dental or orthodontic intervention is done in children diagnosed with cancer, it is important to holistically assess the situation, taking into consideration the advice that has already been given as well as the care plan established in conjunction with the parents. Do not hesitate to get involved in patient care by contacting the child's referring medical team.

RECOMMENDATIONS

Table I shows several different situations that facilitate our discussion of the orthodontic treatment of cancer patients.

In orthodontic practice, several situations may arise:

- children diagnosed with cancer require orthodontic treatment but nothing is done: abstinence is followed here.
- children require orthodontic treatment; the oral examination and radiographic and cephalometric assessments are performed, but when treatment is to begin, cancer is found. No treatment is performed and is deferred. To facilitate the reimbursement of treatment after the 15-year prescribed period has passed, the file must indicate the following in

writing: "suspension of treatment for medical reasons."

- children are being treated at the time of the discovery of the disease. At CHU Rennes, regardless of the phase of orthodontic treatment, it is suspended. The multiring device is removed. We explain below why active orthodontic treatment is not continued during the therapeutic phases of the disease.
- children are in the contention phase. Several alternatives may be proposed (see below).
- children had cancer or are in remission or the orthodontic treatment can be performed but with certain precautions (see below).

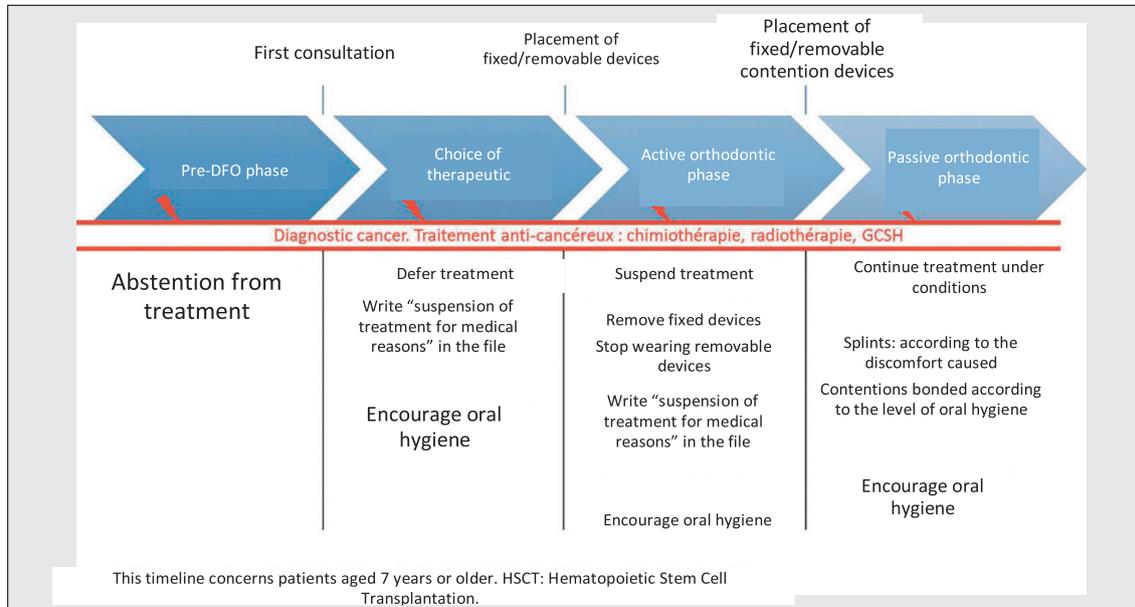
JUSTIFICATIONS/CONSIDERATIONS

Active Orthodontic Treatment and Cancer Therapy

Active orthodontic treatment during cancer treatment is prohibited^{3,6,8,11,19,21},

although, in some hospitals, braces and brackets are not systematically removed¹⁵. Some considerations point to the need to discontinue active orthodontic treatment during cancer therapy.

Table 1: Cancer therapy management based on the orthodontic situation of patients.



Physiopathological Considerations

The mechanism of action of chemotherapy is to target cells with a high rate of cell division, such as tumor cells. Anticancer drugs do not distinguish between tumor cells and normal cells. Many tissues can be affected, such as the buccal mucosa, where basal epithelial cells have a high degree of division (Fig. 1). As a result of cell renewal, the epithelium of the oral cavity becomes thin, which makes it vulnerable to the slightest microtrauma. Erosions/ulcerations of the mucous membranes, constituting mucositis, are frequently observed during chemotherapy.

The physiopathological mechanism of these lesions is not yet fully deciphered. Mucositis is currently described in five biological phases²³ (Fig. 1). The clinical picture (Figs. 2 and 3) shows mucositis. Fig. 3 is largely complicated by dental plaques and irritants in the

oral cavity (cavities, bracket, overflowing amalgam).

Chemotherapy, which is sometimes combined with radiotherapy, reduces the regenerative capacity of the mucosa²⁴, and any irritant can cause chronic oral ulceration, which is a major infectious risk for patients^{3,11}.

Similar to radiotherapy, chemotherapy severely affects the salivary glands and leads to qualitative and quantitative changes in salivary flow^{12,14}. Certain drugs, or their metabolites (as in the case of methotrexate) may be secreted into the saliva²⁰. Xerostomia and high viscosity of saliva have an impact on salivary pH, buccal flora composition, and plaque formation.

Bone metabolism is often disrupted with the administrations of corticosteroids associated with chemotherapy, and bone balance may be negative with the predominant recruitment of osteoclasts. Bone growth is difficult to control.

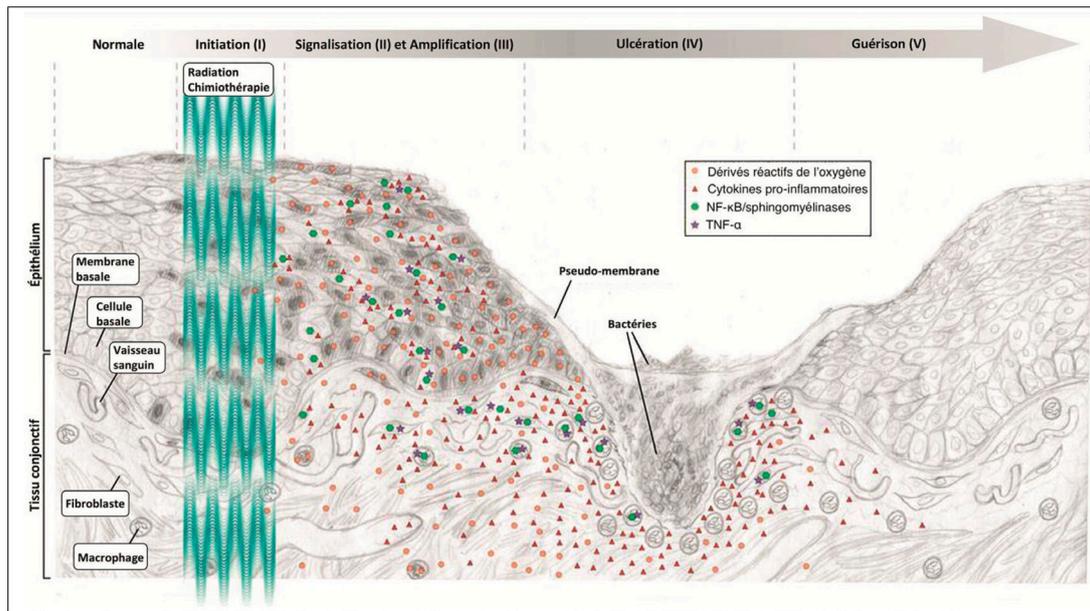


Figure 1

The five biological phases of mucositis (from Sonis ST²⁴). The initiation phase (I) corresponds to the exposure of tissues to drugs or the irradiation of tissues. Anticancer treatments generate reactive oxygen derivatives in tissues. The signaling cascade (II) and amplification (III) phases designate the molecular reactions generated by these compounds. They involve major signaling pathways (NF-κB) and inflammatory messengers (cytokines or TNF-). From a certain threshold of cellular and tissue damage, observable clinical signs occur: erosion and then ulceration (IV). In addition, spontaneous healing (V) of the lesions is initiated by the extracellular matrix of the underlying connective tissue.



Figure 2

Erythema and erosion of the jugular mucosa. The posterior areas of the cheeks, which face the upper molars, are very frequently affected. The yellow color is due to the intake of Fungizone. (Credit: É. Boyer)



Figure 3

Ulceration of the mucosal slope of the upper lip. The labial mucous slopes are at risk of mucosal lesions. A whitish pseudomembrane such as that observed here often covers the ulcerations. (Credit: É. Boyer)

There is a constant risk of infection during cancer treatment; if all infected sites are to be eliminated, the number of sessions with dentists as well as orthodontists must be reduced. As a result, repeat visits for orthodontic follow-ups are unnecessary.

Psychosocial Considerations

The time when the diagnosis is announced is very stressful for patients and their families. Like all health professionals, orthodontists must be sensitive to the emotional implications of the diagnosis of a hematologic or tumor malignancy. By deciding to discontinue active treatment, most often in an emergency, patients and their families may be reluctant to consent. This is particularly true if dental esthetics are still being attained or if the orthodontic treatment is nearing its end. This problem must be treated with the utmost sensitivity.

The consultation involves patients and their parents, under the guise of family physicians and dentists, so that all are informed that the discontinuation of orthodontic treatment is in the best interest for patients^{11,19}. If necessary, orthodontists inform patients and their parents that stopping the treatment results in recurrence or "relapse" of the original dental movements. They have to point out that this is a temporary shutdown: once chemotherapy is completed and patients are in remission, orthodontic treatment can be resumed. The comfort and safety of patients during chemotherapy are improved if all orthodontic appliances are removed³. During this session, orthodontists motivate patients to pay

attention to oral hygiene and remind patients of how important it is to precisely follow the protocol of oral care provided by the center for cancer treatment (Table II shows the hygiene protocol after oral surgery from the Department of Pediatric Hematology–Oncology of CHU Rennes).

Administrative Considerations

Any suspension in DFO treatment and the reason given for it must be well documented in patients' files to facilitate future reimbursements on the resumption of treatment. If devices are removed by a third party, patients are obligated to inform orthodontists.

Clinical Considerations for Orthodontists

- In case of orthodontic treatment with glued or sealed parts

This is an emergency and must be accepted as there is a narrow intervention window. Ideally, intervention should take place between the moment of discovery and the start of chemotherapy, i.e., during the medical inquiry phase (status report of the inquiry, with complementary biological examinations, imaging etc.) Some patients present with such a medical emergency that their cancer therapy is started immediately without allowing any time to stop orthodontic treatment. For these patients, devices are removed during the intertreatment interval. Device removal involves the following:

- pain management: in certain cancerous cases (lymphomas), teeth can be extremely sensitive; the removal

- of brackets and braces must be done while keeping the tooth in position to avoid mobilizing it in its alveolus
- careful polishing: the glue and cement are carefully removed. Any residue can irritate the spine and cause plaque retention.
- encourage the children
- do not give a prescription without informing or discussing it with the referring medical team after informing the parents.
- write a letter stating your advice and what to do at the end of cancer treatment.

- In case of active removable devices, because of disrupted bone metabolism and the need for orthodontic monitoring with frequent appointments, it is advisable to suspend the device for up to 2 years after remission^{15,21}. The alternative of wearing the device after the difficult phases of chemotherapy has shown little success. Very often, patients, even the most motivated ones, abandon the idea of carrying their device because of the pain it causes, the

lesions it generates, or simply because of dental movements; the device is not comfortable or no longer fits the teeth.

Passive Orthodontic Treatment and Cancer Therapy

When the disease is discovered, the active orthodontic treatment has already been completed and is in the restraint phase, either by splints or by bonded restraints.

Depending on the severity of the illness, the ages of children, their wishes and motivations, and the risk of oral lesions, restraining splints may be worn. Experience shows that if splints are worn at the beginning of cancer treatment, they are soon abandoned due to nausea, mouth lesions, changes in taste, and dry mouth.

However, if splints are worn, they must be thoroughly cleaned. When they are not in the mouth, they must be completely immersed in a chlorhexidine solution, which must be replaced daily to avoid any risk of contamination.

Table 2: Oral hygiene protocol of the Department of Pediatric Hematology–Oncology of CHU Rennes.

	Excluding aplastic anemia	In case of aplastic anemia	In case of HSCT
Toothbrush	With supple bristles	Postsurgical	Postsurgical and sterilized
Fluoride toothpaste	Yes	No	No
Chlorhexidine mouthwash	If an oral lesion exists.	Systematic	Systematic
Rinse with 1.4% sodium bicarbonate	Yes	Yes	Yes
Antifungal (oral)	By medical prescription	By medical prescription	Systematic

The head of the toothbrush is kept in a Hextril® flask and rinsed with mineral water before brushing. HSCT: hematopoietic stem cell transplantation.

Restraints bonded to incisivo-canine areas or even up to the first premolar are left in place during chemotherapy, provided oral hygiene is adequate and well maintained. Patient monitoring remains necessary.

Restraints bonded with glue to each tooth of the incisivo-canine block are not as easily tolerated, particularly if it is a twisted arc. Irrespective of the type of bonded restraint, removal may be necessary in severe cases of gingival hyperplasia (linked to immunosuppressive therapy, such as ciclosporin) or insufficient oral hygiene.

Orthopedic and Orthodontic Care after Cancer Therapy

Before resuming orthodontic treatment, it is advisable to inquire about the end date of cancer therapy and other ongoing therapies. Antibio prophylaxis and the use of immunosuppressants are signs that there are still risks of infection.

Two years after HSCT, orthodontic treatment can be resumed or started. At this stage, acute complications are rare, and immunological reconstitution is achieved²¹. For chemotherapy that does not require radiotherapy or transplantation, orthodontic treatment may begin or be resumed a few months after the end of treatment. Children or adolescents are taken care of.

Radiotherapy can have an impact on craniofacial growth. Irradiation of the chondrocranium or synchondroses has a cytotoxic effect on chondrocytes and decreases their vascularization⁷. Children who have undergone cervical, cervicospinal, or orofacial irradiation or ICT in their infancy are affected by this growth-suppressing effect. In a study

on 17 children irradiated with ICT, Dahlöf et al. have shown a reduction in the vertical dimensions of the face, alveolar processes, as well as the sagittal dimensions of the bones⁵.

In a study conducted by Sonis et al. on 97 children, the authors have shown increased mandibular retrognathism in irradiated children before the age of 5 years²². The most commonly accepted side-effects of radiotherapy are short, slender roots, which are prone to resorption during tooth displacement^{2,6,16,17}. Orthodontists are very vigilant in this regard and should shorter roots be the case, apply less force.

Chemotherapy and/or radiotherapy are implicated in case of dental abnormalities, particularly cases of taurodontism and agenesis¹³. These anomalies most often concern children with early onset cancers (before the age of 5 years). Central nervous system tumors can be linked to the common embryology between the teeth and the central nervous system. Odontoblasts originate from neural crest cells and undergo the same deregulation. Thus, abnormalities in the Wnt signaling pathway disrupt neurogenesis and odontogenesis, leading to neuroblastoma formation and dental agenesis¹.

Today, significant progress is being made in the treatment of pediatric cancers, allowing hundreds of thousands of children to survive into adulthood, and most of them require orthodontic treatment. In addition to prognostic improvements, the side-effects of anticancer therapies are decreasing. Orthodontists can play a role in this decrease by learning about the orofacial and dental complications of pediatric cancer therapies. This knowledge is necessary and needs to be updated to be cognizant

of the guidelines for the treatment of such patients. The absence of national recommendations encourages further research to be conducted by specialized and interregional teams.

Consequently, even if each dentist or orthodontist only has a few questions about a specific patient or patients,

we still recommend that concerned professionals should not hesitate to contact the referring medical team to be duly informed of the medical situation of children and the potential local recommendations that have been established by the regional network of pediatric hematology–oncology¹⁰.

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