

CASE REPORT

Long-term Adverse Effects of Acute Myeloid Leukemia Treatment on Odontogenesis in a Child

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ABSTRACT

Background: Several studies showed that cancer therapies during tooth development are associated with dental abnormalities, including enamel defects, arrested tooth development, microdontic teeth, and agenesis.

Study design: We describe the case of a nine-year-old boy treated for acute myeloid leukemia at 15 months of age, who presents several dental abnormalities resulting from anticancer treatment.

Results: The patient was included and treated according to the ELAM 02 French protocol. Six years after allogeneic hematopoietic stem cell transplantation, the intraoral and radiographic examination highlighted the agenesis of the second permanent molars and three of the four second premolars, microdontia of the first premolars, root stunting of the central incisors and first premolars, rootlessness of the first permanent molars, and enamel defects localized at the permanent incisors and canines. As a first step to reduce enamel defects, restorations with resin composite (Tetric EvoCeram® A2, Ivoclar Vivadent) were performed under a dental dam. Orthodontic treatment was contraindicated due to arrested tooth development, short roots, and a risk of resorption is considered too important.

Conclusion: The young age at diagnosis (<5 years of age) and intensive chemotherapy (especially myeloablative conditioning with high doses of cyclophosphamide and Busulfan) could explain the severity of the dental abnormalities. This case illustrates the importance of systematically scheduling a dental follow-up in parallel with the onco-hematologic follow-up allowing the clinicians to prevent, detect, and propose early intervention for dental late effects.

Keywords: Childhood cancer, Long-term survivors, Tooth abnormalities.

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INTRODUCTION

Over the past decades, the survival rate for childhood cancer has increased substantially. This can be explained by more effective chemotherapy regimens. Improvement in survival has led to delayed emergence of sequelae in long-term survivors such as heart failure, infertility, or risk of secondary malignancy. Furthermore, several studies have shown an association between cancer treatments such as radiotherapy and/or chemotherapy and dental developmental abnormalities, including agenesis, root stunting, and enamel defects. Indeed, radiation interferes with the dental development by directly inhibiting the mitotic activity of odontoblasts. Although the risk of dental abnormalities after radiotherapy is well described, the factors associated with long-term dental effects after chemotherapy for childhood malignancies are less known. Chemotherapies received during dental development affect odontogenesis and amelogenesis in childhood malignancy survivors. These anomalies are described in children treated for solid tumors¹ or hematological malignancies² such as acute lymphoid leukemia. Although these anomalies represent half of childhood cancers, acute myeloid leukemia (AML) occurs only in 15 to 20% of acute leukemia cases³ and long-term side effects involving tooth development are not often reported. Here, we report the case of a nine-year-old boy treated for AML at 15 months of age, who presents several dental abnormalities resulting from anticancer treatments.

CASE DESCRIPTION

A young patient was diagnosed with acute myeloid leukemia (AML) at 15 months of age. He was included and treated according to the ELAM 02 French protocol. This treatment protocol contains induction chemotherapy with aracytine and novantrone, each course lasting

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7 days and 5 days, respectively. The first complete remission was obtained so that the induction chemotherapy was followed by three courses of consolidation chemotherapy. The patient received aracytine, amsacrine, daunorubicin, etoposide, and l-asparaginase. Six months after the end of chemotherapy, a bone-marrow relapse was diagnosed. The patient received a new induction chemotherapy with the FLAG scheme (fludarabine, high-dose aracytine, and G-CSF). Due to poor response, a second-line induction chemotherapy with the IDAFLAG scheme (idarubicin, fludarabine, and high-dose aracytine) was administered to the patient, leading to a complete response. The doses of chemotherapeutic agents are listed in Table 1. Allogeneic hematopoietic stem cell transplantation (allo-HCT) was then performed after a myeloablative conditioning, including busulfan (1.2 mg/kg/ × 4 per day × 4 days) and cyclophosphamide (50 mg/kg/day × 4 days). The patient received cyclosporine, methotrexate,

Table 1: Doses of chemotherapeutic agents according to the patient received

Induction chemotherapy		
Aracytine		200 mg/m ² /day × 7 days
Novantrone		10 mg/m ² /day × 5 days
Consolidation chemotherapy		
No. 1	Aracytine	3 g/m ² × 2/day × 3 days
	Amsacrine	100 mg/m ² × 2/day × 3 days
No. 2	Aracytine	200 mg/m ² /day × 4 days
	Daunorubicine	40 mg/m ² /day × 4 days
	Etoposide	100 mg/m ² /day × 4 days
No. 3	Aracytine	3 g/m ² × 2/day D1, D2, D8, D9
	L-asparaginase	6000 U/m ² /day D2, D9
FLAG		
	Fludarabine	30 mg/m ² /day from D2 to D6
	Aracytine	2 g/m ² /day from D2 to D6
	G-CSF	From D1 to D6
IDAFLAG		
	Idarubicin	8 mg/m ² /day D2, D4, J6
	Fludarabine	30 mg/m ² /day from D2 to D6
	Aracytine	2 g/m ² /day from D2 to D6
	G-CSF	From D1 to D6

and anti-thymoglobulin for graft vs host disease (GvHD) prophylaxis. He developed grade II-acute gastrointestinal tract and skin GvHD treated with steroids and mycophenolate mofetil, and then extensive chronic GvHD (gut, skin, and lungs), which required multiple immunosuppressive drugs (mycophenolate mofetil, infliximab, rituximab, tacrolimus, basiliximab, and steroid therapy for 2 years) associated with extracorporeal photochemotherapy, antibiotic prophylaxis (amoxicillin), and anti-viral drug (zovirax). The patient also suffered from pulmonary aspergillosis and mucormycosis treated with antifungal therapy (amphotericin B, voriconazole, caspofungin).

Six years after allo-HCT, the patient was referred to the Department of Pediatric Dentistry. The intraoral examination revealed structural anomalies such as enamel defects located at the permanent maxillary and mandibular central and lateral incisors and canines (Fig. 1A).

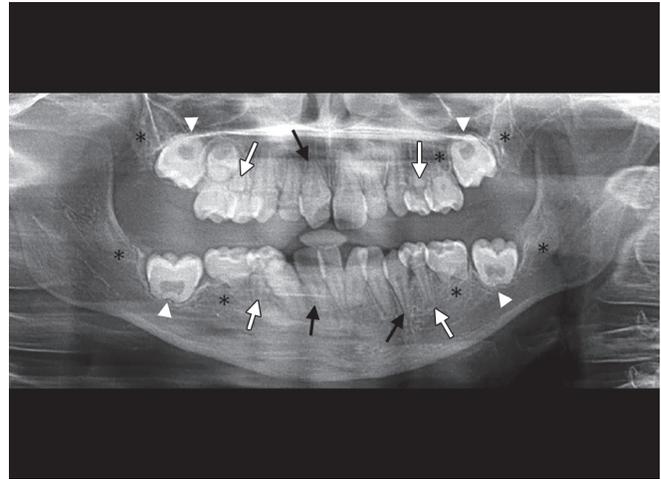


Fig. 2: Dental panoramic radiograph: agenesis of the second permanent molars and three second premolar (asterisks), microdontia of the first premolars (white arrows), root stunting of the maxillary and mandibular central incisors and first premolars (black arrows), and rootlessness of the first permanent molars (arrow heads) in a nine-year-old patient treated for AML

The dental panoramic radiograph (Fig. 2) showed several dental developmental abnormalities including agenesis of the second permanent molars and three second premolars, microdontia of the first premolars, root stunting of the maxillary and mandibular central incisors and first premolars, and rootlessness of the first permanent molars. Dental examination was completed by an orthodontic examination for advice regarding his malocclusion. Orthodontic treatment was contraindicated due to the arrested tooth development and short roots. The risk of root resorption was considered too important. As a first step to reduce enamel defects, we proposed to perform restorations with resin composite (Tetric EvoCeram® A2, Ivoclar Vivadent) after micro-abrasion realized under a dental dam (Fig. 1B). The patient and his parents accepted only the restorations of the permanent maxillary incisors and canines. A systematic scheduling of a dental follow-up in parallel with the onco-hematologic follow-up was established. The objectives were (1) maintaining the primary teeth on the dental arch as long as



Figs 1A and B: (A) Enamel defects located at the permanent incisors and canines in a nine-year-old patient treated for AML with chemotherapies and allo-HCT at 15 months of age; (B) Resin composite restorations (Tetric EvoCeram® A2, Ivoclar Vivadent) of the permanent maxillary incisors and canines 9 months after the restorations were performed

possible (initiate a preventive treatment that contains application of fluorinated varnish and filling the grooves of the occlusal face for example, the purpose being to avoid the development of carious lesions), (2) observing the eruption of permanent teeth to detect structural anomalies, (3) evaluating the mobility of permanent teeth with short roots, (4) proposing a prosthetic treatment to replace missing teeth, prevent disorders in orofacial functions and promote the bone growth, and (5) meeting expectations of the patient and his parents. On the prosthetic plan, a removable prosthesis could be indicated and must be regularly adjusted to the bone growth. The bone remodeling process and the bone growth are considerable and do not allow the placement of implant during this period of growth. Implant therapies must be postponed and considered when the bone growth is complete.

DISCUSSION

Proc *et al.*⁴ showed that dental abnormalities were most frequently observed in cancer survivors than in healthy patients (62% vs 13%, p value < 0.0001). Cytotoxic molecules at the time of early dental development may result in agenesis, microdontia, and enamel defects, while effects of antineoplastic agents in the later stages of formation are characterized by the anomalies of root formation.⁵⁻⁷ Considering the sequence of dental calcification and development,⁸ children between 0 and 5 years of age seem to be at the highest risk of several dental abnormalities resulting from anticancer treatments. Indeed, several studies reported an age-specific risk for dental abnormalities.^{5,9-11} This explains the important number of missing teeth and the enamel defects observed in our patient, who received cancer treatment at 15 months of age.

It is given that chemotherapies include several molecules, and it is difficult to determine the independent effects of each antineoplastic agent on dental anomalies. However, previous studies have identified that cyclophosphamide and vincristine are associated with dental developmental disturbance in the survivors of childhood malignancies.^{1,9,10} Furthermore, several studies reported that children conditioned with total body irradiation (TBI) and high dose chemotherapy (cyclophosphamide and busulfan) before HCT are at high risk for dental developmental abnormalities.^{12,13} Considering this data, our patient, who received myeloablative doses of busulfan and cyclophosphamide for HCT, was at a high risk for long-term several dental abnormalities. His clinical picture confirms this hypothesis. It has also been suggested that the early use of antibiotics (amoxicillin) under the age of 4 years can disturb dental hard tissue formation and lead to enamel defects such as molar incisor hypomineralization (MIH),¹⁴ but the etiology of MIH is still unclear. In our patient, antibiotic prophylaxis (amoxicillin) was associated with the treatment of the GvHD from 2.5 to 8 years of age. To date, there has been no reported case of dental abnormalities such as agenesis, root stunting, microdontic teeth or enamel defects associated with immunosuppressive therapy in children. This case clearly illustrates the extent of oral late side effects of anticancer treatment in the survivors of childhood cancer and confirms that the severity of dental abnormalities is influenced by both younger ages at chemotherapy and by high doses of some antineoplastic agents and maybe some antibiotic and immunosuppressive therapies.

The impact of odontogenesis disturbance is also psychological. Dental anomalies in childhood cancer survivors are obviously not life-threatening complications, but they can impair the quality of life of teenagers and young adults. The occurrence of these dental anomalies is a reminder of cancer pathology, as they are a visible

stigma. Dental anomalies decrease masticatory functions, maxillary bone growth, and may lead to orthodontic troubles but also impact the aesthetic view of the anterior region, especially enamel defects. A study showed that young people may make negative psychosocial judgments on the basis of enamel appearance.¹⁵ Enamel defects should not be ignored and the practitioner should pay attention to the dental anomalies as far as the appearance of some enamel defects can be improved by simple non-invasive procedures such as micro-abrasion and composite restorations.¹⁶

More knowledge into the prevalence of these adverse late effects and risk factors associated is necessary to determine and prevent dental abnormalities to inform and provide support to the patient and his family.

CLINICAL SIGNIFICANCE

A twice yearly dental examination carried out by a dental surgeon experienced in survivorship care, as recommended by the Children's Oncology Group guidelines,¹⁷ should be a part of medical follow-up monitoring late effects in long-term survivors of childhood cancer. This case illustrates the importance of systematically scheduling a dental follow-up in parallel with the onco-hematologic follow-up allowing the clinicians to prevent, detect, and propose early intervention of dental late effects.

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