Journal of Advances in Medicine and Medical Research

Volume 36, Issue 7, Page 77-85, 2024; Article no.JAMMR.118357
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Dental Radiographic Alterations in Patients Undergoing Antineoplastic Therapy in Childhood: A Case Series

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i75487

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/118357

Case Study

Received: 09/04/2024
Accepted: 13/06/2024
Published: 18/06/2024

ABSTRACT

Introduction: Antineoplastic therapy (AT) can cause unwanted effects, including dental alterations. However, many of the studies are case control or cohort studies, use a big number of patients, and may make it difficult to discuss the individual sequels.
Objective: Therefore, this article aims to describe five cases of patients who had done AT in childhood or adolescence and discuss the radiography alterations. The side effects related were agenesis (five patients), root anomalies (two patients) and microdontia (two patients). This individual case analysis enabled to discuss chemotherapeutic agents and radiation parameters individually and the age of dental formation when the patient did the AT.
Conclusion: In these cases, only when the therapy was perform in the age of teeth formation it was consider a direct effect of AT, so the cases presents root malformations, microdontia and premolars

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Cite as: Longo , Bruna C., Isabel B. Rohling, Pauline L. M. O. E. Silva, Maria D. B. de Souza, and Cléverson O. Silva. 2024. "Dental Radiographic Alterations in Patients Undergoing Antineoplastic Therapy in Childhood: A Case Series". Journal of Advances in Medicine and Medical Research 36 (7):77-85. https://doi.org/10.9734/jammr/2024/v36i75487.

agenesis and third molars agenesis. On the other hand, another cases of root malformations, microdontia and third molars agenesis may be an indirect effect of AT or caused by other external factors, because the AT was not performed at the age of formation of these teeth.

Keywords: Antineoplastic protocols; dental radiography; drug effects; neoplasm; tooth abnormalities.

1. INTRODUCTION

The term cancer is used to describe uncontrolled cell growth diseases, childhood cancer (CC) includes neoplasm that affects zero to 19 years old patients. There were an estimated 8.460 new cases of CC in Brazil in 2020 [1] being this disease considered rare compared to adult cancer [2]. However, as in developed countries, in Brazil, CC represents the leading cause of death from disease among children and adolescents aged 1 to 19 years [1].

In the last decade progress in treating childhood and adolescent cancer has been extremely significant; around 80% of CC cases can be cured [1]. In addition, the antineoplastic therapy depends on the neoplasia type and the disease stage [1]. This treatment aims to inhibit neoplastic cell proliferation, mainly during the mitotic phase; however, other tissues, such as oral/gastrointestinal mucosa, bone marrow and skin cells, present similar proliferation states, which contribute to unwanted effects [3]. In such a way, approximately two-thirds of CC survivors have at least one late effect resulting from antineoplastic therapy (AT) [4]. However, there are varied amounts of drugs used for AT, which affect the body in different ways, presenting diverse unwanted effects [2]. Therefore, more attention is being given to the long-term effects of AT, particularly on dental tissue [5,6].

As far as we know, many effects of AT are irreversible [3,5]. Patients undergoing treatments during tooth development (4 months of intrauterine life to early adolescence) have increased risk to oral effects like agenesia [7,8], microdontia [8], crown/root malformation [7,9] enamel hypoplasia or discoloration [7,10,10a].

Moreover, a systematic review demonstrated that these patients could show some dental defects and younger age at CC diagnosis and treatment are associated with higher prevalence of dental defects [5]. However, there is a lack of studies focused on the individual analysis of patients, such as case series, specifying the AT and dental effects. The big number of patients (case control or cohort studies) may make it difficult to individually discuss the effect of each chemotherapeutic agents and radiation parameters with the age of dental formation. Therefore, this article aims to describe five cases of patients who had done AT in childhood or adolescence and discuss the radiography alterations and your relationship with the age of teeth formation when the patients received the AT.

2. CASE PRESENTATIONS

This case series describes five patients who had done antineoplastic therapy in childhood or adolescence and, sometime after finishing the treatments, had their X-rays evaluated for alterations or abnormalities. Patients' radiography alterations are summarized in Table 1. These patients were selected in a project at UOPECCAN Hospital. This study protocol was submitted to and approved by the Human Research Ethics Committee of State University of Western Parana (UNIOESTE) (4.244.416) and UOPECCAN Hospital (121/2020). All participants signed an informed consent form after receiving explanations regarding the nature, potential risks, and benefits of the study.

All radiographs were evaluated by two researchers individually (BCL and COS) and in case of divergence, a third evaluator (MDBS) carried out the evaluation. The objective of the article was to evaluate tooth and tooth-support structures. Analysis of restored areas or radiolucent areas suggestive of caries were not mentioned.

2.1 Case 1

Male patient, evaluated at 13 years and 10 months old. This patient had undergone treatment for medulloblastoma at 5 years old that included a protocol of chemotherapy: VCR, IFO VP (ifosfamide and vespid) and carbo VCR (carboplatin and vincristine) for 19 months. He also received radiotherapy, 5400 cGy divided on 46 sessions in the brain region. Fig. 1 represents the patient's radiography, which showed agenesis of teeth 38 and 48. The third molars initiate formation at around 7 years old [11] near

the age of AT (patient finished the AT at 6 years and 7 months).

2.2 Case 2

Male patient, evaluated at 11 years and 9 months old. This patient had undergone treatment for Rhabdomyosarcoma at 4 years and 11 months old that included a protocol of chemotherapy: VCR, VCR/ACT/IFO (vincristine, dactinomycin andIfosfamide) and ciclo vinerabline (ciclofosfamida and vinorelbina) for 17 months. The radiotherapy was 5400 cGy divided into 30 sessions in the cervical region. Fig. 2 represents the patient's radiography, which showed root anomalies in inferior teeth and agenesis of teeth 38 and 48. The root formation of inferior teeth started at 3 years old [11] and patient started the AT at 4 years and 11 months. The third molars initiate formation at around 7 years old [11] near the age of AT (patient finished the AT at 6 years and 4 months).

Fig. 1. Case 1 radiography (Agenesis of 38 and 48)

Fig. 2. Case 2 radiography (Root anomalies in inferior teeth and agenesis of 38 and 48)

Table 1. Radiography alterations in patients

Clinical case	Sex	Age at treatment	Assessmentage	Neoplasm type	Treatment type	Radiography Alteration
1	Male	5 years	13 years 10 months	Medulloblastoma	Chemotherapy+Radiotherapy	Agenesis
2	Male	4 years 11 months	11 years 9 months	Rhabdomyosarcoma	Chemotherapy+Radiotherapy	Root anomalies and agenesis
3	Female	2 years 8 months	9 years 7 months	Acute lymphoid leukemia	Chemotherapy	Root anomalies, agenesis and microdontia
4	Female	2 years 2 months	8 years 8 months	Wilms tumor	Chemotherapy	Agenesis and microdontia
5	Female	2 years 1 months	10 years 6 months	Wilms tumor	Chemotherapy	Agenesis

Fig. 3. Case 3 radiography (Root anomalies in teeth 34, 35, 44 and 45, microdontia in teeth 37 and 47 and agenesis of 18, 28, 38 and 48)

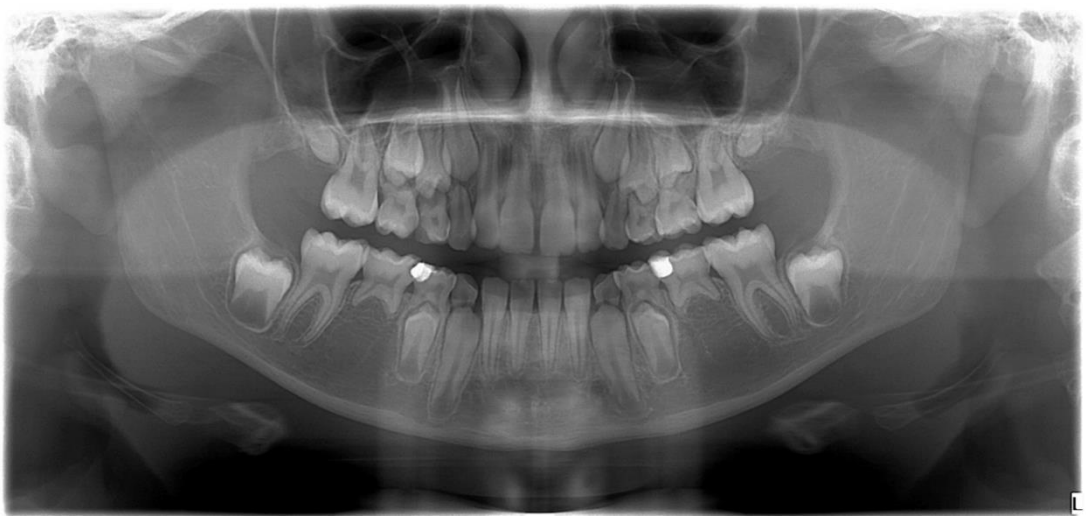

Fig. 4. Case 4 radiography (Agenesis of 18, 28, 35, 38, 45 and 48 and microdontia of teeth 17 and 27)

2.3 Case 3

Male patient, evaluated at 9 years and 7 months old. This patient had undergone treatment for Acute lymphoid leukemia at 2 years and 8 months old, that include a protocol of chemotherapy: induction (daunorubicin, vincristine and asparaginase), consolidation D28 (mercaptopurine, cyclophosphamide and cytarabine), intrathecal (methotrexate and cytarabine), low risk intensification (mercaptopurine and methotrexate), late consolidation (vincristine, cytarabine, cyclophosphamide, fauldoxo and mercaptopurine), phase 1 maintenance (mercaptopurine and methotrexate) and phase 2 maintenance (vincristine, mercaptopurine and methotrexate) for 24 months. Fig. 3 represents the patient's radiography, which showed root anomalies in teeth 34, 35, 44 and 45, microdontia in teeth 37 and 47 and agenesis of teeth 18, 28, 38 and 48. The root formation of premolars started around at 7 years old [11], patient finished the AT at 4 years and 8 months. The crow formation of inferior molars started the formation at 3 years old [11], age of patient did the AT. The third molars initiate formation at around 7 years old [11], 3 years later the AT.

Fig. 5. Case 5 radiography (Agenesis tooth of 18)

2.4 Case 4

Female patient, evaluated at 8 years and 8 months old. This patient had undergone treatment for Wilms tumor at 2 years and 2 months old, that included a protocol of chemotherapy: carbo VP (carboplatin and etoposide), block A (mercaptopurine, methotrexate, cyclophosphamide and cytarabine) and CICLO/DOXO (cyclophosphamide and doxorubicin) for 8 months. Fig. 4 represents the patient's radiography, which showed agenesis of teeth 18, 28, 35, 38, 45 and 48 and microdontia of teeth 17 and 27. The inferior premolars started the formation at 3 years old [11] near the age that patient did the AT. The third molars initiate formation at around 7 years old [11], 4 years later the AT. The superior molars started the growth at 4.3 years old [11], and the patient finished the AT at 2 years and 10 months.

2.5 Case 5

Female patient, evaluated at 10 years and 6 months old. This patient had undergone treatment for Wilms tumor at 2 years and 1 month old, that included a protocol of chemotherapy: VCR, Neuro IX (cyclophosphamide and topotecan) and VCR/ACT (vincristine and dactinomycin) for 8 months. Fig. 5 represents the patient's radiography, which showed agenesis of tooth 18. The third molars initiate formation at around 7 years old [11], 4 years later the AT.

3. DISCUSSION

The present report shows five childhood cancer patients' X-rays who developed oral side effects after antineoplastic treatment. As far as we know, this is the first study to consider the age of teeth formation and the dental effects. The side effects related in this case series were agenesis (cases 1, 2, 3, 4 and 5), root anomalies (cases 2 and 3) and microdontia (cases 3 and 4). In these cases, chemotherapy (CH) and chemoradiotherapy possibly changed the tooth development, since the antineoplastic agents are cell unspecific and they do not differentiate healthy cells from neoplastic ones [3]. The dental effects of antineoplastic agents are very unique because the teeth, different from the other bony structures, do not undergo remodeling [5].

In the 80's, a rat study showed that antineoplastic drugs might inhibit odontogenesis [12]. Up to now, new evidence attests the CH effects on dental tissue development and show the drug influence on it [5,13]. In this sense, literature mentions actinomycin D, doxorubicin (adriamycin), vinblastine and vincristine as possible drugs with effects on tooth structures. For example, the first two agents caused the rats pre-odontoblasts death [14,15]. Moreover, doxorubicin reduced the number of live human teeth pulp cells and fibroblasts [14,15]. Indeed, studies suggested vinblastine and vincristine-induced dental tissue alterations (quantitative and qualitative), and that they would affect both odontoblasts [16] and mature secretory ameloblasts [3]. One of the reported patients were treated with doxorubicin (case 1) and four (cases 1, 2, 3 and 5) were treated with vincristine. All dental alterations observed in the patients were shown in Table 1. The extension of effects will depend not only on the chemotherapeutic agent type, but also on the number of susceptible cells during the use of the drug [17]. It is clear that the dental development process reaches its highest activity during 3 to 5 years old [18]. In that way, in this case series, all patients did the therapy in this age and showed some dental development alterations - microdontia, agenesis and root anomalies.

Similar to CH, the younger the child the lesser the resistance to the ones which are more radiosensitive [5,13]. Another important fact is the dose and area of radiation. For cases 1 and 2 dose and area of radiation were, respectively, 5400 cGy, brain region and 5400 cGy, cervical region. A radiation dose-dependent effect on tooth development alterations was suggested, and higher doses of radiation (18-24 Gy) increase the risk of defects development [5]. These two patients received high doses of radiation and showed some dental alterations (root anomalies in mandible and agenesis). In case 1, the RT was in the head (brain), but not directly in the dental area, which also could explain the presence of only localized dental alteration (agenesis). In case 2, the RT was in cervical region and the patient showed significant root anomalies. Is important to remember that these two patients also received CH, so the dental alterations could be caused by RT, CH or both.

A systematic review that included 1300 patients reported that the most common root and crown defects were impaired root growth and microdontia, respectively [5]. Root anomalies (cases 2 and 3) were present in those who underwent treatment between 2 and 4 years old, and microdontia (cases 3 and 4) were present in those who underwent treatment at 2 years old. It

is important to consider that dental development occurs from 4 months intrauterine until the tooth completes formation in early adolescence [11]. The age of the patients initiating the AT in this case series ranged from 2 to 5 years old, and, as previously mentioned, the highest activity of dental formation is during 3 to 5 years of age. In such way, the AT might have interrupted dental growth by affecting ameloblasts and odontoblasts [18]. In addition, another study suggests that patients that did AT before 7 years old had more risk to develop dental abnormalities [19].

Furthermore, it is important to consider the relationship between tooth formation at the age the patient received AT. In the case 2, root anomalies were present in inferior teeth, and he started the AT at 4 years and 11 months old and finished at 6 years and 4 months old, exactly the time of root formation of inferior teeth [11]. However, it is different from case 3, that showed root anomalies in inferior premolars, and he started the AT at 2 years and 4 months and finished at 4 years and 4 months, the age at which the crown is formed and not the root [11], which is formed at age 7 years. On the other hand, in this same case the patient showed microdontia of 37 and 47, teeth in stage 2 of growth (initial calcification) [11] at the momento of AT. The case 4 showed microdontia of teeth 17 e 27, however these teeth started the growth at 4.3 years old (1.8 nolla stage), and the patient finished the AT at 2 years and 10 months. Therefore, it can be inferred that the AT may have directly affected the root formations in the case 2 and microdontia in the case 3. Root malformations in the case 3 and microdontia in the case 4 may be due to an indirect effect of TA, a variation in time of tooth formation or caused by other external factors.

Another disturbance in dental development observed in this case series was agenesis of third molars (18, 28, 38 and 48) and premolars (35 and 45). Literature agrees that this alteration is more prevalent in CC individuals compared with the healthy one [3,7,8,9]. Although all patients presented agenesis of third molars, it is important to cite that third molars agenesis could be common in a non-syndromic population (5923 Patients - 38.4%) [20]. Once again, when ages of teeth formation were considered, the third molars initiate formation at 7 years old [11]. In this case, AT could have directly influenced in its formation only in cases 1 and 2, in which patients finished the AT near this age. The other cases (case 3, 4 and 5), the agenesis may be an indirect effect of AT or caused by other external factors. On the other hand, the agenesis of teeth 35 and 45 in the case 3, can be due to the AT direct effect, because these teeth initiate the formation in the age in which patient had done the AT [11].

Finally, this case series suggest the AT can interfere in dental development, however, other factors, such as hereditary or genetic factors can also affect dental alterations and need be considered. In addition, it is important to consider a variation in time the tooth formation and the age of patients, because the Nolla stage is a mean of the age formations [11] not a rule, so the AT may have affected the tooth formation in the cases in which it was not carried out near the age. Possibly, the main limitation of this case series was the limitations of panoramic radiographs (inherent artifacts and distortion in the image), however, this type of radiograph is the most adequate for the age of the studied patients, as well as presents a general overview of teeth and supporting structures.

4. CONCLUSION

This paper discussed dental radiographic alterations in five patients undergoing AT and patients showed: agenesis, microdontia and root anomalies. However, when the age of teeth formation was considered, only root malformations in inferior teeth in case 2, microdontia in case 3, premolars agenesis in case 3 and third molars agenesis in cases 1 and 2 was a direct effect of AT, because the therapy was being carried out in age of teeth formation. On the other hand, the other alterations, root malformations in case 3, microdontia in case 4 and third molars agenesis in case 3, 4 and 5 can be indirect effect of AT or caused by other external factors, because these teeth is not in formation when the AT was done. However, we should also keep in mind that a variation in the age of teeth formation is also a possibility. In such way, we suggest that future studies consider the age of teeth formation during the use of AT.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

All participants signed an informed consent form after receiving explanations regarding the nature, potential risks, and benefits of the study. All authors declare that a written informed consent was obtained from the patients for publication of this study.

ETHICAL APPROVAL

This study protocol was submitted to and approved by the Human Research Ethics Committee of State University of Western Parana (UNIOESTE) (4.244.416) and UOPECCAN Hospital (121/2020).

ACKNOWLEDGEMENTS

To the Coordination for the Improvement of Higher Education Personnel (CAPES) for granting the scholarships involved in this project.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Instituto Nacional do Câncer (INCA). Tipos de câncer: Câncer infantojuvenil; 2022. Available:https://www.inca.gov.br/tipos-de-cancer/cancer-infantojuvenil. Accessed June 2022.
2. Grabow D, Kaiser M, Hjorth L, Byrne J, Alessi D, Allodji RS, et al. The Pan care sur fup cohort of 83,333 fiveyear survivors of childhood cancer: a cohort from 12 European countries. Eur J Epidemiol. 2018;33(3):335-349. DOI:10.1007/s10654-018-0370-3.
3. Çetiner D, Çetiner S, Uraz A, Alpaslan GH, Alpaslan C, Toygar Memikoğlu TU, et al. Oral and dental alterations and growth disruption following chemotherapy in long-term survivors of childhood malignancies. Support Care Cancer. 2019;27(5):1891-1899. DOI:10.1007/s00520-018-4454-0.
4. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572-1582. DOI:10.1056/NEJMsa060185.
5. Seremidi K, Kloukos D, Polychronopoulou A, Kattamis A, Kavvadia K. Late effects of chemo and radiation treatment on dental structures of childhood cancer survivors. A systematic review and meta-analysis. Head Neck. 2019;41(9):3422- 3433.
6. Busenhart DM, Erb J, Rigakos G, Eliades T, Papageorgiou SN. Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: A systematic review with meta-analysis. Oral Oncol. 2018;83:64-72.
7. Alpaslan G, Alpaslan C, Gögen H, Oğuz A, Cetiner S, Karadeniz C. Disturbances in oral and dental structures in patients with pediatric lymphoma after chemotherapy: a preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(3):317-21.
8. Pedersen LB, Clausen N, Schrøder H, Schmidt M, Poulsen S. Microdontia and hypodontia of premolars and permanent molars in childhood cancer survivors after chemotherapy. Int J Paediatr Dent. 2012; 22(4):239-43.
9. Nemeth O, Hermann P, Kivovics P, Garami M. Long-term effects of chemotherapy on dental status of children cancer survivors. Pediatr Hematol Oncol. 2013;30(3):208-15.
10. Avşar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 104(6):781-9.

10a. Van der Leij S, Lebbink CA, Lentjes EG, Tissing WJ, Stuart AV, van den Heuvel-Eibrink MM, van Santen HM, van Dalen EC. Thyroid dysfunction during treatment with systemic antineoplastic therapy for childhood cancer: A systematic review. Critical Reviews in Oncology/Hematology. 2023;103958.

11. Nolla CM. The Development of the Permanent Teeth. Journal of dentistry for children. 1960;4:254-266.
12. Mataki S. Comparison of the effect of colchicine and vinblastine on the inhibiton of dentinogenesis in rat incisors. Arch Oral Biol. 1981;26(12):955-61.
13. Gawade PL, Hudson MM, Kaste SC, Neglia JP, Constine LS, Robison LL, et al. A systematic review of dental late effects in survivors of childhood cancer. Pediatr Blood Cancer. 2014;61(3):407-16.

DOI:10.1002/pbc.24842.
14. Lyaruu DM, van Duin MA, Bervoets TJ, Wöltgens JH, Bronckers AL. Effects of actinomycin D on developing hamster molar tooth germs in vitro. Eur J Oral Sci. 1997;105(1):52-8.
15. Jones TE, Henderson JS 3rd, Johnson RB. Effects of doxorubicin on human dental pulp cells in vitro. Cell Biol Toxicol. 2005;21(5-6):207-14.
16. Olczak-Kowalczyk D, Krasuska-Sławińska E, Brożyna A, Turska-Szybka A, Dembowska-Bagińska B. Dental Caries in Children and Adolescents During and After Antineoplastic Chemotherapy. J Clin Pediatr Dent. 2018;42(3):225-230.
17. Näsman M, Forsberg CM, Dahllöf G. Long-term dental development in children after treatment for malignant disease. Eur J Orthod. 1997;19(2):151-9.
18. Carrillo CM, Corrêa FN, Lopes NN, Fava M, Odone Filho V. Dental anomalies in children submitted to antineoplastic therapy. Clinics (Sao Paulo). 2014; 69(6):433-7.
19. Kılınç G, Bulut G, Ertuğrul F, Ören H, Demirağ B, Demiral A, et al. Long-term Dental Anomalies after Pediatric Cancer Treatment in Children. Turk J Haematol. 2019;36(3):155-161. DOI:10.4274/tjh.galenos.2018.2018.0248.
20. Sujon MK, Alam MK, Rahman SA. Prevalence of Third Molar Agenesis: Associated Dental Anomalies in Non-Syndromic 5923 Patients. PLoS One. 2016;11(8):e0162070.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/118357