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Evaluation of the Impacts of Chemotherapeutics on Odontogenesis Process: Findings from a Systematic Review

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Abstract

This study aimed to examine and recognize the impacts of antinoplastic chemotherapeutics on the development of dental germ, employing a systematic review. A retrieving in the literature was carried out, using several medical and scientifical databases (ClinicalKey, Cochrane Library, Google Scholar, MedLine, PubMed, and ScienceDirect), by two investigators separately. In the end of this systematic search, eight articles met the required criteria for inclusion and, therefore, composed the results. Among these, four articles are about observational studies in humans, and the other four about experimental animal studies. In both cases and species, anomalies such as microdontia, hypodontia/agenesia, and root shortening were observed. The severity and frequency varied according to the nature of the chemotherapeutics applied as well as the administered dosage and the patient's age at the time of first exposure. Through the results, it was possible to show the direct impacts of chemotherapy on the odontogenesis process as well as factors such as the type of chemotherapy, the age of the individual at the time of first exposure and the dosage used. All of those should be taken into account when choosing a therapeutic protocol for an oncology patient. Besides, we observed the need for more studies in this area and that these should be standardized in order to allow an objective and direct analysis of comparable parameters, even when different approaches are used.

Keywords
- dental anomaly
- amelogenesis
- chemotherapy
- evidence-based dentistry
- oral health

Introduction

Cancer is a condition characterized by the absence of cell-cycle control in which the cells begin to divide without stopping and spread into surrounding tissues.[1] It ranks in Brazil as the main cause of death due to illness among children and adolescents from 1 to 19 years old, and it corresponds to between 1 and 4% of all malignant tumors in the population.[2,3] However, these are considered rare when compared to cancer in adults.[4] It is estimated that nearly 3,000 people died in 2013, and more than 12,600 new cases were recorded in 2017.[5]

Chemotherapy has a significant role in the treatment of cancer patients. The determination of a therapeutic protocol involves the administration of drugs. The process of the drug being used, alone or combined, for the treatment of diseases caused by biological agents, and/or when it is used in neoplastic processes, is referred to as antineoplastic chemotherapy.[5,6] It is

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indicated for rapidly developing neoplasias, such as leukemias, carcinomas, breast tumors, osteosarcoma and renal tumors.[7–9]

The general action mechanism of chemotherapeutics is cytotoxicity, by interfering with the cell's vital metabolic functions and, thus, leading to lysis. Drugs are classified according to their mechanism of action and origin; the main ones are alkylating agents, antimetabolites, natural products (vinca alkaloids and taxanes), antibiotics, L-asparaginase enzyme, and hormones.[10–12] Although they act with higher sensitivity in tumor cells, most chemotherapeutics have nonspecific performance. The drugs may damage both atypical and native cells in healthy tissues, especially those with high mitotic activity, such as cells from the hematopoietic system, mucosal cells,[13,14] and tissues that are developing during childhood and adolescence, such as bones and teeth.[15]

Mucositis, xerostomia, trismus and dental anomalies may be listed among some oral complications that are critical.[15–19] Stawinska et al[20] correlated enamel hypoplasia with the use of vincristine and methotrexane, as well as the occurrence of opacities with the use of vincristine, cisplatin, methotrexate, doxorubicin, and carboplatin in children within the mean age of 12 years old. Microdontia, color changes, taurodonticism and decreased root length were observed as a proliferative delay. Inhibition of odontoblasts and dentin-forming cells occurred in children and adolescents treated with vincristine, ara-C, docetaxel, carboplatin, and mercaptopurine.[17,21,22]

Most cancer treatment regimens tend to use two or more chemotherapeutics in alternating or concomitant synergistic activity,[22–24] which, in addition to other intrinsic and extrinsic factors, makes it difficult to determine the exact effect of the drug in odontogenesis and its direct impact on dental structure.[17] Some analyses may be better performed in controlled environments. *In vitro* studies, for example, demonstrated the activity of vincristine on the dental germs of hamsters, such as dose-dependent interference of amelogenic mineralization and induction to incomplete nuclear polarization during differentiation of ameloblasts and odontoblasts. However, they had little effect on mature secretory cells, prevalent in germs that are in later stages of development.[25]

The use of antineoplastic chemotherapeutics affects the development of dental germ, thus bringing masticatory, occlusal and aesthetic complications for the patient. It is extremely important to understand which ones cause more significant damage to odontogenesis and how it occurs, making it possible to guide future clinical protocols, aiming to give cancer patients a better quality of life and oral health.[20,23,26,27]

Therefore, the purposes of this study were: 1) to perform a systematic review of studies that examine and recognize the antineoplastic impacts of chemotherapeutics on developing dental germs, 2) to get to know which drugs could show more significant activity in odontogenic tissues and 3) to find out how these two combined knowledge could guide future therapeutic protocols suggesting approachings that are able to provide a treatment with lower toxicity to dental tissues but keeping the life-saving effectiveness as priority. This knowledge will also assist in providing insights for the construction and application of systematic reviews in the dentistry scenario.

Material and Methods

This systematic review is being analyzed by the International Prospective Register of Systematic Reviews (PROSPERO) database, with a view to being accepted for a possible future publication in the aforementioned directory, under the following ID number: 102906.

Questions for Clinical Research

What are the impacts of chemotherapeutic approaches on oral health? May different chemotherapeutic protocols affect dental development? May chemotherapy be a source of dental disorders?

Patient/Problem, Intervention, Comparison, Outcome (PICO) Statement

The PICO statement[28] used was the following:

P – Patients, problem or population: Cancer patients after antineoplastic treatment and laboratory mice exposed to chemotherapy;
I – Intervention: Collection of anomalies found in oncological patients and in laboratory animals that have been exposed to chemotherapy;
C – Comparison: The influence, from a histological and clinical viewpoint, of chemotherapeutic agents on dental germ in both populations studied;
O – Outcome: Evidence of factors that, together with the use of chemotherapeutic agents, influence the development of dental germs.

Protocol Used

This systematic review followed the Prefered Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[29]

Elegibility Criteria

The articles were included in the current systematic review if the studies met all the following criteria divided into two classifications (I – Studies performed in humans; II – Studies performed in animal model).

I–1) identification of the chemotherapeutic agent(s) used; 2) description of treatment protocol adopted; 3) period of exposition to chemotherapy is specified; 4) identification of the patient's age during treatment; 5) description of changes in dental germ reported.
II – 1) laboratory test; animals were randomly assigned to the control and intervention groups; 2) the chemotherapeutic agent utilized is identified; 3) period of exposition to chemotherapy and dosage are specified; 4) description of changes in dental germ reported.

The studies that did not have two or more of the aforementioned points were excluded.

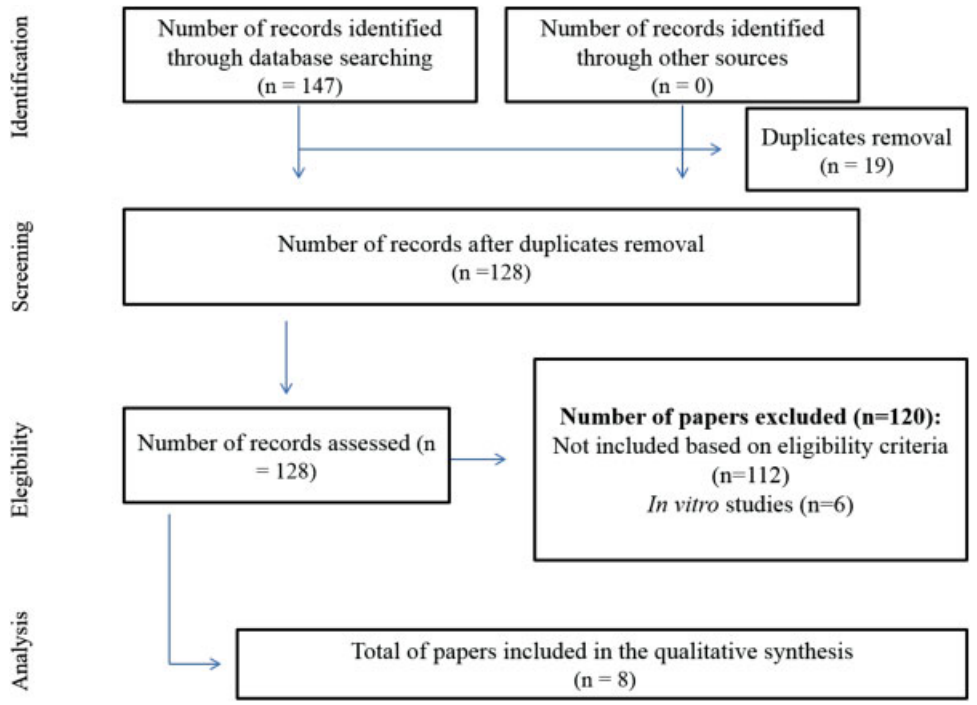

Fig. 1 Flow diagram for identification, screening, elegibility and analysis of studies included in this current systematic review.

Search Strategy

Several electronic databases were used to search for articles that were published before May 2018. The authors have chosen six databases: ClinicalKey, Cochrane Library, Google Scholar, MedLine, Pubmed, and Science Direct, using the combination of the following terms: ("chemotherapeutic agents" OR "chemotherapeutic drugs" OR "chemotherapy") AND ("tooth" OR "tooth development" OR "dental development' OR "dental germ"). Two independent investigators performed the systematic search and evaluated the abstracts of papers found; any possible disagreement was resolved by a third investigator. The references of papers included were screened for potential additional studies that could be relevant.

Data Collection and Analysis

All studies included within the chosen criteria were processed for data extraction by two investigators that followed a standardized protocol as follows: author, year of publication, type of research, type of sample, sample N, control N, chemotherapy used, protocol (for humans) and dose administered (in animals), radiotherapy included, period of exposition, dental changes observed and proposals of treatments to minimize the damages.

Methodologic Quality

The risk of bias was assessed through use of the Cochrane Collaboration's tool[30] and The Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) tool.[31] They assessed the methodological quality of the papers included and, therefore, the presence or absence of potential bias.

Characteristics of Papers Included

The present study identified 147 articles and, after the steps of screanning and selection, eight papers remaind. Five from them were excluded. 3 papers would compose the results; however, five additional papers have been identified from the evaluation of the references presented in included papers. Therefore, 8 articles remained in the results (►**Figure 1**).

Among the eight articles assessed, five were studies using human models, two of them being studies of case reports,[32,33] one observational sectional study[34] and a longitudinal one[35]; four of them were related to animal studies, all of them standardized laboratory tests.[36–39] The results found in each study were separated into two groups, the first one involving laboratory tests with animal models and the second one with human studies (►**Tables 1**, **2**, **3**, **4**).

Sensitive Analysis and Risk of Bias

To identify potential failures in methodologic strategies used in the studies included, the risk of bias was assessed. The Cochrane Collaboration's tool was used to analyze the studies with humans and the SYRCLE's tool to assess the risk of bias in the studies with animals. The results were shown in ►**Figure 2** and ►**Table 5**.

This systematic review summarizes the effects of some of the most significant influences of chemotherapeutic agents on the development of the dental germ as regards to histological and clinical aspects. The administration of antineoplastic chemotherapeutics directly affects the development of the dental germ and may cause lysis of undifferentiated odontogenic and mesenchymal cells. Also, interruption of cell cycle and loss of morphology and secretory activity; its ability to recover function and morphology appears to be less

Table 1 Methodological aspects from studies in animals

First author/Year	Study	Sample type	N control	N control	Chemotherapeutic	Dosage	Exposure time	Age	Weight of samples
Adatia (1975)	Laboratory research	Wistar rats	9	3	Cyclophosphamide (Alkylating agent)	40 mg/kg	single dose	*	250–400g
						80 mg/kg			
						120 mg/kg			
Adatia (1981)		Wistar rats	14	10		40 mg/kg	single dose	*	250g
			16	12		40 mg/kg/day	8 days		
Kawakami (2015)		IRC rats	16	16		100 mg/kg	single dose	12 days	*
Vahlsing (1975)		Albino rats	10	100		75 mg/kg	single dose	6 weeks	*

Table 2 Methodological aspects from studies performed in humans

First author/year	Study	N sample	Chemotherapeutics	Protocol	Radiation	Treatment time	Age	Bone-marrow/ stem-cell transplantation
Dahllof (1994)	case report	1	VCR, ADM, MTX, CYC	CC	*	2 years	2.3 years	performed
					10 Gy	1 year	4.3 years	
Nishimura (2013)	sectional study	26	BUS, CYC, MEL, TIO, MCNU, IFO.	CC	*	M = 2.1 years	M= 3.7 years	not performed
		20		CC + HDC (alkaloid)	12 Gy (n = 6)	M = 1.3 years		performed (n = 7)
Yamamoto (2012)	longitudinal study	11	CYC, VCR, INN-ADM, ETO, CIS, DIC, CBDCA, MEL, ADM, ACNU, CTP-11, IFO	CC	*	M = 11 months	M = 1 year and 5 months	not performed
Zwetchkenbaum (2007)	case report	1	CIT, VCR, CIS, NIT, ADM	CC	3,000 cGy	5 months	2 years	not performed

Abbreviations: ACNU, nimustine; ADM, doxorubicin; BUS, busulfan; CBDCA, carboplatin; CC, conventional chemotherapy; CIS, cisplatin; CIT, citroxane; CTP-11, irinotecan; CYC, cyclophosphamide; DIC, dacarbazine; ETO, etoposide; HDC, conventional chemotherapy with high dose chemotherapy; IFO, ifosfamide; INN, pirarubicin; M, mean; MCNU, ranimustine; MEL, melphalan; MTX, methotrexate; NIT, nitrogen mustard; TIO, thiotepa; VCR, vincristine.

predictable with an increased dosage.[13,32,38] Observable later effects are: eruptive disorders, mesiodens, dentinomas, hypoplasia, taurodontia, root shortening, microdontia or agenesia of a tooth or group of teeth, more often present in patients submitted to high dose treatment protocols.[16,20,27,40]

Adatia,[36] in his experiment with Wistar rats, observed histological changes in the organization, morphology, reproductive capacity, and a degree of cell regeneration, dividing the groups by different doses (40, 80 and 120 mg/kg) and by counting days after exposure (1, 4 and 8 days). The frequency and severity of the anomalies presented are directly proportional to the doses that were administered, undifferentiated cells or mitotic activity were the most affected: germs exposed to cisplatin at the dose of 40 mg/kg showed a capacity to restore basal morphology and continuity of rhizogenesis. Dental germs exposed to doses of 80 mg/kg and 120 mg/kg showed delayed regeneration and did not resume basal odontogenesis; therefore, a more extended follow-up is necessary to ascertain the reproductive regenerative capacity of mesenchymal cells even at high doses. In another study, Adatia and Berkovitz[37] obtained similar results when a single dose of 40 mg/kg cyclophosphamide was administered in the rodent group. Variables related to dentin regularity, periodontal ligament density and continuity of the epithelial sheath were also considered. In both studies, the incisors represented the group of teeth analyzed.

Kawakami et al,[38] in their study of 12-day-old albino rodents that were exposed to 100 mg/kg cyclophosphamide, considered the variables of root length, apical foramen area and the number of odontoblasts in the cervical and apical portions of the pulp. They were followed from the 16th until their 27th day of life. In a summary of the results obtained, the authors described premature closure of the apical foramen, root shortening, and cell number reduction. On the other hand, Vahlsing's et al[39] performed the only study on animals that did not have histological considerations. The author reports certain eruptive irregularities, such as agenesis/ hypodontia, supernumerary teeth, and delay of incisor teeth eruption, after the application of 75 mg/kg cyclophosphamide in 6-week-old albino rats, followed up by a period of 7 months.

Only two studies presented a quantitative evaluation of the results;[37,38] these could not be simultaneously compared because they assessed different aspects of the same outcome,

Table 3 Main findings extracted from studies in animals

First author/ Year	Developmental changes observed				
	Effects on the dental germ				Late effects on the tooth
Adatia (1975)	1 d		4d	8d	*
	Disintegrated cells with a large, multiple or fragmented nucleus in the zone of undifferentiated mesenchymal cells near the basal epithelium; differentiated cells in the pulp and unaffected ameloblasts, without obvious modifications		Root growth arrest; acellular area in the pulp below the basal dentin; apparently normal pulp near the acellular area in the 40 mg group; acellular area in the pulp with extension to the odontogenic epithelium in the 80 mg group	Normal basal dentin and enamel formation plus root growth resumption in the 40 mg group; odontogenesis not yet recorded in the 80 mg group; acellularity in the basal pulp extended to the odontogenic epithelium in the 120 mg group	
Adatia (1981)	Single dose group				Significant delay of eruptive rates
	On the 3rd day; acellular areas in the pulp; areas of pulp destruction, odontogenesis suspension on vestibule and lingual surfaces, irregular dentin, lower density and incisive reorientation of the periodontium		On the 6th day: acellular areas closer to the basal pulp, morphological aspects close to normality; irregular dentin near a region where temporary odontogenic activity was stopped	On the 8th day: irregular dentin near a region where temporary odontogenic activity was stopped; epithelial sheath loss in the lingual portion of the germ	
	Multiple dose group				
	On the 3rd day: pulp acellularity, atrophy of the enamel organ, odontogenesis suspension and cytotoxicity signs		On the 6th day: greater areas of pulpal acellularity and hemorrhage, marked atrophy on odontogenic epithelium, irregular dentin, reduction of cell density in the periodontium		
Kawakami (2015)	16 d	20 d	24 d	27 d	*
	lengths of the distal root (μm): 615 ± 52 (CG); 679 ± 29 (EG)	lengths of the distal root (μm): 950 ± 60 (CG); ~ 830 ± 50 (EG)	lengths of the distal root (μm): 1,150 ± 20 (CG); ~ 750 ± 20 (EG)	lengths of the distal root (μm): 1,213 ± 48 (CG); 769 ± 14 (EG)	
	apical foramen area (mm^2): 0.14 ± 0.02 (CG); 0.12 ± 0.06 (EG)	apical foramen area (mm^2): 0.10 ± 0.005 (CG); 0.04 ± 0.02 (EG)	apical foramen area (mm^2): 0.09 ± 0.02 (CG); 0.03 ± 0.015 (EG)	apical foramen area (mm^2): 0.07 ± 0.03 (CG); 0.02 ± 0.015 (EG)	
	16d -> number of odontoblasts (cel/100μm): CG - 11.0 ± 1.8 (cervical portion) and 13.0 ± 0.8 (apical portion); EG - 9.1 ± 1.5 (cervical portion) and 10.6 ± 1.3 (apical portion);				
Vahlsing (1975)	*				Root shortening or complete loss of incisors; elongation of extreme incisors, supranumerary incisor development

Abbreviations: CG, control group; EG, experimental group.

Table 4 Main findings from studies performed in humans

First Author/year	Dental development changes	Proposals to minimize the damages of chemotherapeutics on the tooth
Dahllöf (1994)	Irregular dentin, root shortening in all teeth, premature apical closure, enamel hypoplasia and microdontia	Orthodontic fixation
Nishimura (2013)	Agenesis and microdontia; root shortening	*
Yamamoto (2012)	Root shortening, hypodontia and agenesis	*
Zwetchkenbaum (2007)	Dental mobility, little or no root development in the maxillary teeth, agenesis of several teeth and generalized root shortening	Lower removable partial denture, totally removable upper denture and implants

resulting in non-standardized and incomparable values. Finally, only subjective factors remained for critical evaluation, making it impossible to elaborate a meta-analysis.

According to Nishimura et al,[34] the incidence of agenesis/microdontia was significantly higher in the high-dose chemotherapy (HDC) group (n = 10) in patients whose treatments were started when they were less than eight years old when compared to the conventional chemotherapy (CC) group (n = 24). This difference was even more significant for patients who were younger than 4 years old at the

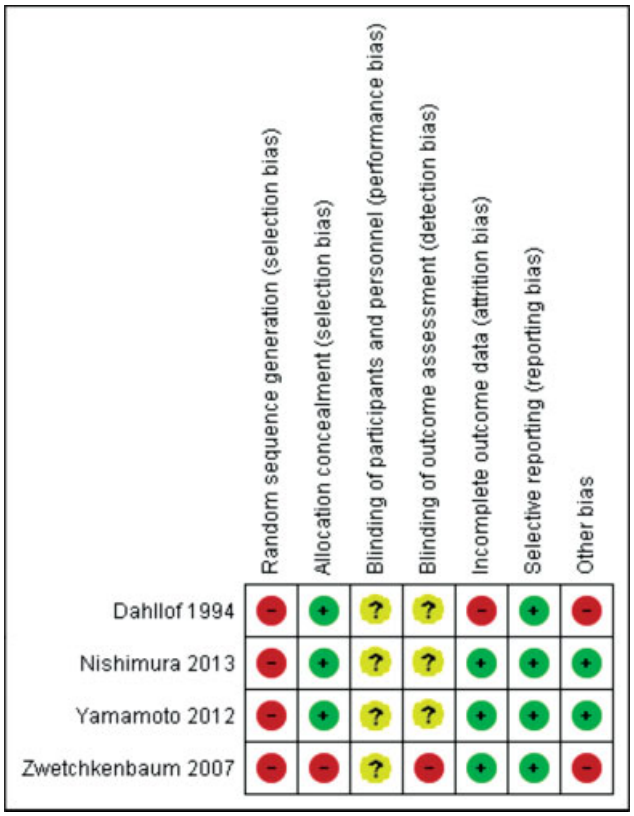

Fig. 2 Risk of bias summary—Review of authors' judgements about each risk of bias. Items for each study included that was performed on humans.

start of CC (n = 15) or CC + HDC (n = 5). Thus, it is understood that the lower the patient's age at the beginning of the treatment, the higher the frequency of dental developmental disorders. In all cases, rates of anomalies during dental development were higher in the HDC group than in the CC group, and the TBI group did not show a significant difference in the rates of tooth formation abnormalities. Besides, among the patients in the HDC group, the rates of defects in those given bussulfurane (n = 7) were significantly higher than for those in which cyclophosphamide (n = 4) had been administered.

The case reports exposed severe developmental dental anomalies in their respective patients. The patient reported by Dahllöf et al[32] had premature foramen closure and root shortening in the second year of observation, with more significant severity in the hemiarcate of the upper left quadrant. Nine years later, the premolars and second molars showed microdontia and generalized disorders in root development. Two teeth, the upper left lateral incisor and the second right upper premolar, were extracted and sent for histological analysis. At the histological examination, the lateral incisor tooth showed normal morphology, but numerous incremental lines in the middle of the cervical portion of the enamel (corresponding to the initial 3 months of intensive treatment with cytotoxic drugs). The second premolar tooth had hypoplasia and tubular dentin irregularity (the location of this change corresponds to the time of the administration of 10 Gy TBI). In the case report described

Table 5 Risk of bias summary: a review of the authors' judgements about each risk of bias item for each study included that was performed on animals

First author/ Year	Selection Bias			Perfomance bias		Detection bias		Attrition bias	Reporting bias	Others
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome	
Adatia (1975)	High risk	High risk	Low risk	High risk	Unclear	High risk	Unclear	High risk	High risk	High risk
Adatia (1981)	High risk	High risk	Low risk	High risk	Unclear	High risk	Unclear	Low risk	Low risk	High risk
Kawakami (2015)	High risk	High risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	High risk
Vahlsing (1975)	High risk	High risk	Low risk	High risk	Unclear	High risk	Unclear	High risk	High risk	High risk

by Zwetchkebaum and Oh (2007), the patient had severe root shortening throughout the maxillary and mandibular dentition, multiple tooth agenesis and severe microdontia. As a consequence, he also presented occlusal plane dysfunction. It is important to note that the patient had also been exposed to craniofacial irradiation during the treatment, possibly aggravating these changes. Both case reports considered the possibility of dental treatment to reduce dental damage, such as orthodontic therapy, dental implants and total denture replacement and/or partial removable prosthesis. All of them are essential options to either keep or improve the patient's quality of life.[26] There was no evidence to correlate the duration of treatment/exposure to defects on the dental germ of patients. However, the laboratory tests showed that the sample groups that were subjected to more than one application of cyclophosphamide presented a delay in odontogenesis when compared to the group that received a single application.[33,34,38] The presence of other adjuvant therapies, such as stem-cell and bone-marrow transplantation, was mentioned among sample groups and case reports but was not considered for analysis in the studies.

There are many parameters and variables to be evaluated in observational studies of dental anomalies in cancer patients[26,40]; however, there are few standardized studies that allow the development of a robust systematic and statistical analysis. In this systematic review, the elaboration of a meta-analysis was not feasible.

Conclusions

Based on the analysis exposed, the impact of chemotherapy on dental development is evident and these complications can be harmful to the quality of life of the patients. There is a need for standardized human and animal studies that enable a meta-analysis in order to explore the performance of these drugs on dental tissue with and without adjuvant therapies, as well as the possibility of reducing its effects and consequences for cancer patients.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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