Oral Oncology 83 (2018) 64–72

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: A systematic review with meta-analysis

Dan Mike Busenhart[a], Juliane Erb[a], Georgios Rigakos[b], Theodore Eliades[a], Spyridon N. Papageorgiou[a,*]

[a] Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland
[b] Third Oncology Department, Hygeia Hospital, Athens, Greece

ARTICLE INFO

Keywords:
Childhood cancer
Chemotherapy
Adverse effects
Teeth
Tooth agenesis
Caries
Meta-analysis

ABSTRACT

Objective: The aim of this systematic review was to assess evidence on dental adverse effects associated with chemotherapy (CH) administered to children with cancer.

Material and methods: Eight databases were searched without restrictions up to March 2017 for studies reporting on dental effects of CH administered for childhood cancer. After elimination of duplicates, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of Relative Risks (RR) and Mean Differences (MD) and their 95% Confidence Intervals (CI) were performed, followed by meta-regression and sensitivity analyses.

Results: The literature search identified a total of 15 non-randomized case-control studies including at least 2315 patients (mean age at diagnosis or CH of 6.6 years; 36% male) followed for up to 22.9 years after CH. Meta-analysis indicated that CH was associated with increased risk for tooth agenesis compared to healthy controls (RR = 2.47; 95% CI = 1.30–4.71; P = 0.006). This translated to every seventh child with CH having agenesis of at least one tooth that would not otherwise have. Additionally, CH was significantly associated with increased risk of tooth discoloration, arrested tooth development, enamel hypoplasia, microdontia, premature apexification, and decreased salivary flow rate, as well as worse oral hygiene and greater caries experience compared to controls. However, the strength of evidence was very low due to the inclusion of non-randomized study designs with high risk of bias.

Conclusions: Current evidence from childhood cancer survivors indicates that chemotherapy is associated with considerable dental adverse effects that might be associated with greater burden of disease and treatment costs.

Introduction

Rationale

Considerable improvements have been seen during the last decades in the development of effective treatment protocols for childhood cancer, which usually consist of multiagent chemotherapy (CH), radiotherapy, or a combination of both. For example, the cure rate for Acute Lymphoblastic Leukemia (ALL), which is the most common childhood malignancy [1], has increased from less than 30% during the 1960s to an 80–86% 5-year overall survival [2].

Although developments in the curative therapy of childhood cancer have led to dramatic improvements in survival, mortality rates of childhood cancer survivors continue to be elevated for many years beyond 5-year survival compared to the general population [3]. Furthermore, childhood cancer survival is associated with many treatment-related late sequelae with potential effects on physical function including among others neurocognitive dysfunction, cardiopulmonary toxicity, endocrinopathy, and secondary malignancy, the frequency and severity of which depends on sex, age at diagnosis, and cumulative dose-exposures of specific treatment modalities [4–6]. Childhood cancer survivors are also prone to psychological distress that is associated with academic underachievement, underemployment, and functional limitations, which may adversely affect health status [7,8].

Likewise, several studies have assessed the potential impact of childhood cancer and its treatment on oral health status. As such, high prevalence of oral manifestations has been reported among pediatric cancer patients receiving CH that included among others gingivitis [9,10], caries [9–13], mucositis [10,13,14], cheilitis [10], oral pain [14], periodontitis [10], recurrent herpes [10], altered salivary

* Corresponding author at: Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich, Plattenstrasse 11, CH-8032, Zurich.
E-mail address: spyridon.papageorgiou@zzm.uzh.ch (S.N. Papageorgiou).

https://doi.org/10.1016/j.oraloncology.2018.06.001
Received 26 March 2018; Received in revised form 30 May 2018; Accepted 1 June 2018

immunological conditions [12,13], xerostomia [13,14], and disturbances in the number or development of teeth [9,11,12]. These adverse effects might have considerable impact on the functional or psychological status of childhood cancer survivors and ultimately their quality of life, while they may be associated with considerable financial burden. Therefore, the adoption of measures for the prevention or treatment of oral health related complications of childhood cancer treatment might be appropriate.

The current evidence base for any adverse effects of cancer treatment on the teeth of children is rather bleak. Only a single systematic review exists on this subject [15] that has several issues like being outdated, involving questionable a priori design, limited search, inadequate assessment of the included studies risk of bias, and no quantitative synthesis. Additionally, assessed interventions included radiotherapy, CH, and hematopoietic cell transplant treatment, even though evidence for both independent and additive effects of each treatment was found [15]. This makes accurate estimations about the contribution of each therapeutical approach to the development of adverse effects difficult and therefore has limited value from a preventive or therapeutic side.

Aim

Current evidence on short- or long-term dental complications of CH administered to children with cancer is limited. Therefore, aim of the present systematic review was to assess in an evidence-based manner the existing data from clinical studies on humans and try to answer the question: *What are the adverse effects on the dentition and surrounding tissues of CH administered to children with cancer*?

Material and methods

Protocol and registration

The review's protocol was made a priori following the PRISMA-P statement [16], registered in PROSPERO (CRD42017058660), and all post hoc changes were appropriately noted. This systematic review was conducted and reported according to Cochrane Handbook [17] and PRISMA statement [18], respectively.

Eligibility criteria

According to the Participants Intervention Comparison Outcome Study design schema (PICOS), we included both randomized and non-randomized clinical studies on human children up to 18 years of age, sex, or ethnicity with any kind of cancer being treated with CH. The primary outcome of this systematic review was tooth agenesis, while the secondary outcomes included developmental defects of teeth, clinical inflammatory or caries indices, and salivary outcomes. Excluded were non-clinical studies, case reports, animal studies, and all studies where CH is combined with radiotherapy.

Information sources and literature search

Eight electronic databases (MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effects, Virtual Health Library, Scopus, Web of Science, and ClinicalTrials.gov) were systematically searched by one author (SNP) without any limitations from inception up to March 2017 (Appendix 1). Additionally, five sources (Google Scholar, International Standard Registered Clinical/Social Study Number Registry, Directory of Open Access Journals, Digital Dissertations, and metaRegister of Controlled Trials) and the reference/citation lists of included trials were manually searched for any additional trials. No limitations concerning publication language, publication year, or publication status were applied.

Study selection

The eligibility of identified studies was checked sequentially from their title, abstract, and full-text against the eligibility criteria by one person (DMB) and were subsequently checked independently by a second one (SNP), with any conflicts being resolved by a third person (TE).

Data collection and data items

Study characteristics and numerical data were extracted from included studies independently by two authors (DMB, SNP) using predefined and piloted extraction forms including: (i) study characteristics (design, clinical setting, country), (ii) patient characteristics (number, sex, age), (iii) cancer type, (iv) CH type, (v) follow-up after CH, and (vi) outcomes assessed. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was calculated, whenever possible.

Risk of bias in individual trials

The risk of bias of included randomized trials was to be assessed using Cochrane's risk of bias tool [17]. The risk of bias of included non-randomized studies (NRS) was assessed using the Newcastle-Ottawa scale for case-control studies [19].

Outcomes and data synthesis

The primary and secondary outcomes of this review were either binary or continuous and were expressed as Relative Risks (RR) or Mean Differences (MD), respectively with their corresponding 95% Confidence Intervals (CI). Statistically significant results were translated to their Numbers Needed to Treat (NNT) to gauge their clinical relevance.

As adverse effects of CH are bound to be affected by the patient's age, dental/skeletal growth phase, cancer type, CH type or duration, and the patient's immunologic response, a wide variation of true effects was expected and a random-effects model was judged a priori sensible, based on biological, clinical, and statistical grounds [20]. The alternative Paule-Mandel random-effects estimator was used instead of the more widely known DerSimonian and Laird [21] one, based on contemporary guidelines, due to its improved performance [22].

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and calculating the tau^2 and the I^2, respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not by chance [23]. Heterogeneity was roughly categorized as low moderate, and high according to I^2 values of 25%, 50%, and 75% [23], although the heterogeneity's localization on the forest plot was also examined. Additionally, the 95% CIs around tau^2 and I^2 were calculated [24] to quantify our uncertainty around these estimates. 95% predictive intervals were calculated for meta-analyses of ≥ 3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting [25]. All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, Texas, USA) by one author (SNP) and the dataset was made freely available [26]. A two side $P \leq 0.05$ was considered significant for hypothesis-testing, except for $P \leq 0.10$ used for tests of between-studies or between-subgroups heterogeneity [27].

Additional analyses and quality of meta-evidence

Possible sources of heterogeneity were *a priori* planned to be sought through mixed-effects subgroup analyses and random-effects meta-regression for meta-analyses of $\geq$ five studies according to (i) patient characteristics (age, sex, ethnicity, cancer type, phase of dentition, oral health) (ii) preventive or therapeutic interventions administered prior