

Periodontal effects of two innovative oral rinsing substances in oncologic patients

DIANA CRISTALA KAPPENBERG-NIȚESCU¹, IONUT LUCHIAN¹, IOANA MÂRȚU²,
SORINA-MIHAELA SOLOMON¹, SILVIA MÂRȚU¹, LILIANA PĂȘĂRIN¹, ALEXANDRA MÂRȚU¹,
IOANA-ANDREEA SIOUSTIS¹, ANCUȚA GORIUC^{3*} and MONICA TATARCIUC^{2*}

Departments of ¹Periodontology and ²Dental Technology, Faculty of Dental Medicine; ³Department of Biochemistry,
'Grigore T. Popa' University of Medicine and Pharmacy, Iasi 700115, Romania

Received September 16, 2020; Accepted October 16, 2020

DOI: 10.3892/etm.2020.9530

Abstract. Chemotherapy often presents side effects, including oral adverse effects that may interfere with the completion of the oncology treatment, threatening the outcome of the treatment and significantly affecting the quality of life of the patient. The aim of the present study was to evaluate two antiseptic, antimicrobial and antifungal substances that may be used in order to achieve improved oral hygiene and to lower the prevalence of side effects during chemotherapy. Patients were randomly divided into three groups: Placebo, oral rinse with cetrimide and mouth coating with a pharmacy-made compound (nystatin, neomycin and metronidazole). Their oral hygiene and periodontal parameters were determined at baseline and 14 days of use. It was revealed that the most effective clinical results were achieved in the group that used cetrimide mouth rinse that highlighted the best improvements of parameter values, whereas the control and coating-using group did not obtain statistically significant improvements. Cetrimide oral rinse was demonstrated to be an efficient adjunct method in achieving better oral hygiene and improved periodontal parameters in chemotherapy patients. The present study offers an alternative to the commonly used compounds that may present unwanted side effects in patients during chemotherapy, it promotes

the importance of good oral hygiene in the prevention of chemotherapy-induced oral adverse effects and improves the quality of life of the patient.

Introduction

The side effects of chemotherapy often pose an important problem that both patients and medical personnel are confronted with during treatment. The characteristics of cytotoxic agents manifest both systemically and locally, in various degrees of severity with an incidence of up to 100% of chemotherapy cases (1). It is well known that one of the most severe side effects is myelosuppression and the cascade of events generated by it, such as neutropenia, leucopenia, thrombocytopenia and even pancytopenia (2). The resulted immunosuppression significantly increases the risk of infectious complications that have the potential to interfere with chemotherapy outcome and results and threaten the life of the patient (3).

The primary target of chemotherapy drugs are malignant cells; however, considering the lack of cell specificity, these substances interfere with some of the normal tissues as well. The specific tissues affected by chemotherapy present a high turnover cellular rate in the basal layer, including digestive tract mucosa, bone marrow, hair follicle tissue, respiratory tract mucosa and oral soft tissues. The result within the oral cavity is the appearance of mucositis, infections, dysgeusia, hyposialia or xerostomia, and an increased probability of hemorrhage (4).

The periodontal disease represents a multi-factorial condition affecting the supporting tissues of teeth that, in the absence of treatment, leads to a progressive decrease of attachment, tooth mobility and ultimately, tooth loss (5). The bone destruction that occurs is highly correlated with the level of periodontal inflammation and can also be influenced by the interactions between the periodontal pathogenic bacteria, host immune response as well as other factors including infections, chemotherapy, immune suppression (6).

The aim of the present study was to evaluate the effects of two antiseptic, antimicrobial and antifungal products on oral cavity and periodontal tissues in oncologic patients during chemotherapy.

Correspondence to: Dr Ionut Luchian, Department of Periodontology, Faculty of Dental Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, Street Universității 16, Iasi 700115, Romania
E-mail: ionut_luchian@yahoo.com

Dr Ioana Mârțu, Department of Dental Technology, Faculty of Dental Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, Street Universității 16, Iasi 700115, Romania
E-mail: ioanamartu@gmail.com

*Contributed equally

Key words: periodontitis, oncologic patients, chemotherapy, antiseptic, antimicrobial, antifungal

Patients and methods

The study was conducted on 50 subjects with ages ranging between 48 and 60 years old, between November 2015 and October 2016 at the Oncology Clinic of 'Victoria' Hospital in Iași, Romania. The present study was approved by the Ethics Committee of 'Grigore T. Popa' University of Medicine and Pharmacy (Iasi, Romania). All patients included in the sample population signed an informed consent prior to being accepted to take part in this study. The total number of subjects included in the present study consisted of 22 females and 28 males, thus 44% were women and 56% were men, the distribution being similar regarding the sex (Table I). Most patients were from urban areas (90%) and only a small percentage were from rural areas (10%).

Most patients were retired and only 20% were still working or unemployed. The chemotherapy administered to the patients was comprised of cisplatin, oxaliplatin and gemcitabine, the highest frequency of antineoplastic drugs being cisplatin (n=26, 52%), followed by oxaliplatin (n=17, 34%) and gemcitabine (n=7, 14%) (Fig. 1).

The patients included in the present study suffered from systemic cancer, were undergoing chemotherapy and had a form of periodontal disease. In order to avoid compromising the relevance and validity of the results, the following exclusion criteria were considered: i) tobacco smokers; ii) patients with infectious and/or inflammatory disease that may have affected the periodontal status, with the exception of systemic cancer; iii) patients that had had periodontal treatment in the previous 6 months; iv) patients that had had antibiotherapy or anti-inflammatory treatment in the previous 3 months, with the exception of chemotherapy; vi) patients that used antiseptic oral rinses or medical toothpaste.

All subjects were randomly split into three groups: i) controls, which included chemotherapy patients that did not use any active substance throughout the present study; ii) group A, which included chemotherapy patients that used oral rinses with cetrimide mouthwash three times a day; iii) group B, that included chemotherapy patients that used mouth coating with a pharmacy-made compound two times a day.

The clinical examination considered several elements: probing depth (PD), clinical attachment loss (CAL), dental mobility (M), plaque index and periodontal disease index (PDI) In addition, pathological probing depths higher than 3 mm on teeth with no gingival recessions were considered. The clinical examination took place at two time-points: T0, before beginning to use the active substances and T1, after 14 days of antiseptic, antimicrobial and antifungal substance usage.

The two substances evaluated in the present study were Citrolin oral rinse and an oral coating recipe developed at the pharmaceutical laboratory BabyFarm, Ltd. Citrolin is an oral rinsing solution that contains 25 mg cetrimide, 3 mg lidocaine and excipients per 100 ml of product and is administered in the form of oral rinses 15 ml per rinse, three times a day. The oral coating substance was developed in collaboration with BabyFarm, Ltd. laboratory and its composition contains neomycin, nystatin, metronidazole, sodium bicarbonate, vitamin A, xylene 2% and oleum helianthi.

The three groups were evaluated based on oral hygiene and periodontal status before the commencement of oral rinse use and oral coating and 14 days after use. None of the patients declared any side effects after using the two compounds included in the present study.

The statistical analysis of the data included in the present study consisted of descriptive statistics, one Sample t-test and a paired Sample t-test using the SPSS software version 21.0 (IBM Corporation). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The paired Sample t-test revealed a high statistical significance of improvements for group A that used Citrolin oral rinse, the positive modification of all parameters being statistically significant ($P < 0.05$), with the exception of dental mobility, as revealed in Table II.

The results obtained for the controls revealed an increase in the values of all analyzed indices and periodontal disease progression. The modifications of values for these indices had statistical significance with the exception of the average tooth mobility value that had no statistical significance ($P = 0.077$) (Table III). Similarly, group B that used oral coating did not exhibit any improvement of the indices evaluated (data not shown).

Moreover, CAL values were different for each of the three chemotherapy agents included in the study between T0 and T1. The average value of CAL was increased in patients treated with oxaliplatin (mean difference = -0.239) and cisplatin (mean difference = -0.19) (data not shown).

Discussion

The efficiency of antineoplastic treatment with platinum-based drugs (cisplatin, oxaliplatin) has been demonstrated multiple times in the past (7,8), although what does sometimes limit their dosage is their potential side effects. Patients treated with one of these chemotherapy agents may develop up to 40 specific adverse reactions. The most important and frequent effect is nephrotoxicity in the case of cisplatin administration and neurotoxicity in the case of oxaliplatin alongside the well-known myelosuppressive effects (1).

Ideally, periodontal disease should be assessed and treated before the beginning of chemotherapy, bearing in mind that a pre-chemotherapy evaluation and maintaining good oral hygiene has been demonstrated to be efficient in preventing oral and systemic complications during anti-neoplastic treatment (9). Frequent erythematous lesions, ulcerations or candidiasis can occur in the oral cavity during chemotherapy (3). Moreover, modifications of periodontal parameters can be observed through an increase in the quantity of oral bacterial plaque, an exacerbation of gingival inflammatory signs and even modifications of the bacterial community composition at oral and periodontal levels (10).

The use of antimicrobial and antiseptic substances is efficient in plaque reduction and improving periodontal parameters (11). Cetrimide, the active substance in Citrolin, is an antiseptic with multiple quaternary ammonium salts that has a bactericidal effect on a wide spectrum of gram-positive

Table I. Subject distribution in groups according to the oral antimicrobial, antiseptic and antifungal substance used.

Substance	Absolute frequency	Percentage frequency
Placebo (control)	12	24.0
Oral rinse	22	44.0
Oral coating	16	32.0
Total	50	100.0

Table II. Statistical significance analysis for group A, between time-point T0 and T1.

Group A, Citrolin oral rinse T0-T1			
Analyzed indices	Mean difference	t	P-value
Silness-Loe Plaque index	0.092	2.358	0.028
PDI	0.104	2.097	0.048
PBI	0.165	3.578	0.002
Mean dental mobility	-0.045	-1.821	0.083
Mean PD	0.145	4.661	<0.001
Mean CAL	0.161	3.409	0.003

Bold indicates statistical significance. PDI, periodontal disease index; PBI, papillary bleeding index; PD, probing depth; CAL, clinical attachment loss.

and gram-negative bacteria (12). Its action consists of affecting the permeability of the bacterial cellular membrane. It is used in a high number of pharmaceutical compounds with the role to decrease the level of gingival pain and increase oral hygiene (13). It is sometimes used in products that also contain chlorhexidine gluconate (14); however, in the present study, cetrimide was the only active substance in the oral rinse to avoid errors in the results. The use of cetrimide can eliminate bacterial plaque to a great extent, some authors claiming that it has an even higher antimicrobial effect than that of chlorhexidine (15). The effects of cetrimide were also demonstrated to be efficient in preventing carious lesions; a concentration of 0.2% cetrimide used as oral rinse for a minute had the capacity to destroy *Streptococcus mutans* in a proportion of >99% (16).

Conversely, presently, there are available substances with topic application that contain either only metronidazole, or neomycin and prednisolone (17). In the present study, we selected to introduce a new compound with topical administration that contained neomycin and metronidazole with the aim of evaluating its periodontal efficiency. This combination of drugs has been used in the past, but in association with general surgery of the digestive tract. The pre-operative administration was revealed to be an efficient combination of antibiotics that leads to a significant reduction of post-operative infections (18,19).

The most important modifications of the Silness-Loe plaque index were observed in the subjects of group A that

Table III. Statistical significance analysis for controls between time-points T0 and T1.

Quantified indices	Placebo group T0-T1		
	Mean Difference	t	P-value
Silness-Loe Plaque Index	-0.164	-2.680	0.021
PDI	-0.472	-4.513	0.001
PBI	-0.301	-7.473	<0.001
Mean tooth mobility	-0.080	-1.948	0.077
Mean PD	-0.479	-4.823	0.001
Mean CAL	-1.183	-3.467	0.005

Bold indicates statistical significance. PDI, periodontal disease index; PBI, papillary bleeding index; PD, probing depth; CAL, clinical attachment loss.

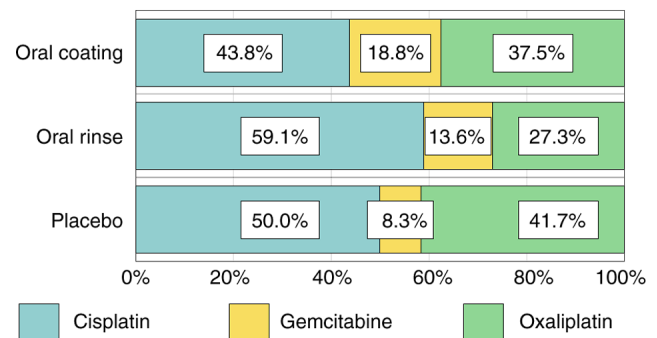


Figure 1. Distribution of the three groups depending on the chemotherapy agent.

used oral rinses with cetrimide. The values of the plaque index were decreased after 14 days of using cetrimide and consequently improved the level of oral hygiene. Conversely, higher values in T1 compared to T0 in the control group (2.002 vs. 1.838) were obtained, thus manifesting an increase of 0.164 between the two evaluations. The values of the plaque index in group B were also increased after 14 days (T1=2.055 vs. T0=1.996) (data not shown).

Another fact for consideration is the medullar modifications that occur during chemotherapy that lead to thrombocytopenia, which can be translated into a pronounced tendency to gingival bleeding in the oral cavity, especially in the conditions of a pre-existing periodontal disease (20). In the study, the PBI exhibited a decrease in value for group A after the 14 days of oral rinsing, signifying an improvement in the periodontal inflammatory status (T1=2.120 vs. T0=2.285; difference =0.165). Then again, controls had higher values of the bleeding index in T1 (T1=2.338 vs. T0=2.037) and group B exhibited similar values at both evaluations (T1=2.206 vs. T0=2.238) (data not shown). These results reflect the modifications obtained for the level of oral hygiene, creating an association between the level of oral hygiene and level of bleeding at the periodontal level.

The average PD obtained in the present study revealed considerable differences between the controls and patients that used antimicrobial/antiseptic/antifungal substances. The highest improvements were observed in group A, which used cetrimide oral rinses. This may be explained by the fact that cetrimide has a higher salivary retention rate than chlorhexidine immediately after the rinse is performed, but decreases more significantly at 4 h than chlorhexidine (21), which is why the patients were recommended to perform the action of rinsing more often than they would otherwise in order to maintain an optimal concentration in the saliva and at the periodontal level.

Oral mucositis and periodontal disease progression are important modifiers for the level of quality of life of patients undergoing chemotherapy and negatively impact the affective state of patients (22), as we have shown in a previous study (23). The present study offers more options regarding the secondary means of oral hygiene that oncology patients can use in order to prevent the progression of periodontal disease and obtain an improved periodontal status during chemotherapy, thus improving their experience during chemotherapy and obtaining an improvement in their level of quality of life (24-26).

It can thus be concluded that cetrimide oral rinses were demonstrated to be the most efficient secondary means of oral hygiene assessed in the present study. Cetrimide oral rinse decreased the level of bacterial plaque and gingival bleeding and it was efficient in preventing the progression of periodontal disease in patients undergoing chemotherapy.

The present results offer new perspectives regarding a reliable alternative to the contemporary-used secondary means of oral hygiene for oncologic patients undergoing chemotherapy. Thus, the periodontal status of these particular patients can be better controlled and their quality of life can be significantly improved.

Acknowledgements

Professional editing, linguistic and technical assistance was performed by Mrs. Irina Radu, Individual Service Provider, certified translator in Medicine and Pharmacy.

Funding

The study was partially funded by the 'Grigore T. Popa' University of Medicine and Pharmacy Iași-Romania, during the PhD studies of Dr Diana Cristala Kappenberg-Nițescu.

Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DCKN, IL, IM, SM and SMS designed the study. AG and MT contributed substantially in drafting the work and revising it critically for important intellectual content. LP, IAS and AM contributed to the data analysis and data interpretation and

edited the final form of the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The present study was approved by the Ethics Committee of 'Grigore T. Popa' University of Medicine and Pharmacy (Iasi, Romania). All protocols were in accordance with the provisions of the Declaration of Helsinki. All patients included in the sample populations signed an informed consent prior to being accepted to take part in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Oun R, Moussa YE and Wheate NJ: The side effects of platinum-based chemotherapy drugs: A review for chemists. *Dalton Trans* 47: 6645-6653, 2018.
2. American Cancer Society: After diagnosis: A guide for patients and families, 2012.
3. Napeñas JJ, Brennan MT, Bahrani-Mougeot FK, Fox PC and Lockhart PB: Relationship between mucositis and changes in oral microflora during cancer chemotherapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103: 48-59, 2007.
4. Pouloupoulos A, Papadopoulos P and Andreadis D: Chemotherapy: Oral side effects and dental interventions -a review of the literature. *Stomatological Dis Sci* 1: 35-49, 2017.
5. Luchian I, Nanu S, Martu I, Martu A, Nichitean G, Kappenberg-Nițescu DC, Gurău G, Stefanescu V, Pasarin L, Tatarciuc M and Solomon SM: The influence of the composite resin material on the clinical working time in fiberglass reinforced periodontal splints. *Mater Plast* 57: 316-320, 2020.
6. Teodorescu AC, Martu I, Teslaru S, Kappenberg-Nițescu DC, Goriuc A, Luchian I, Martu MA, Solomon SM and Mărtu S: Assessment of salivary levels of RANKL and OPG in aggressive versus chronic periodontitis. *J Immunol Res* 2019: 6195258, 2019.
7. Zhou C, Ren S, Zhou S, Zhang L, Su C, Zhang Z, Deng Q and Zhang J: Predictive effects of ERCC1 and XRCC3 SNP on efficacy of platinum-based chemotherapy in advanced NSCLC patients. *Jpn J Clin Oncol* 40: 954-960, 2010.
8. Park SY, Lee JG, Kim J, Byun GE, Bae MK, Lee CY, Kim DJ and Chung KY: Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. *J Cardiothorac Surg* 8: 151, 2013.
9. Chambers MS, Toth BB, Martin JW, Fleming TJ and Lemon JC: Oral and dental management of the cancer patient: Prevention and treatment of complications. *Support Care Cancer* 3: 168-175, 1995.
10. Jensen SB, Mouridsen HT, Bergmann OJ, Reibel J, Brünner N and Nauntofte B: Oral mucosal lesions, microbial changes, and taste disturbances induced by adjuvant chemotherapy in breast cancer patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 106: 217-226, 2008.
11. DePaola LG, Overholser CD, Meiller TF, Minah GE and Niehaus C: Chemotherapeutic inhibition of supragingival dental plaque and gingivitis development. *J Clin Periodontol* 16: 311-315, 1989.
12. Engebretsen KA, Hald M, Johansen JD and Thyssen JP: Allergic contact dermatitis caused by an antiseptic containing cetrimide. *Contact Dermatitis* 72: 60-61, 2015.
13. Elzanfaly ES, Bassuoni YF, Essam HAM and Zaazaa HE: Ion selective membrane electrodes for determination of cetrimide in pure form and in pharmaceutical formulations. *Anal Bioanal Electrochem* 7: 401-414, 2015.

14. Dostie S, Alkadi LT, Owen G, Bi J, Shen Y, Haapasalo M and Larjava HS: Chemotherapeutic decontamination of dental implants colonized by mature multispecies oral biofilm. *J Clin Periodontol* 44: 403-409, 2017.
15. Guerreiro-Tanomaru JM, Nascimento CA, Faria-Júnior NB, Graeff MS, Watanabe E and Tanomaru-Filho M: Antibiofilm activity of irrigating solutions associated with cetrимide. Confocal laser scanning microscopy. *Int Endod J* 47: 1058-1063, 2014.
16. Ruiz-Linares M, Ferrer-Luque CM, Arias-Moliz T, de Castro P, Aguado B and Baca P: Antimicrobial activity of alexidine, chlorhexidine and cetrимide against *Streptococcus mutans* biofilm. *Ann Clin Microbiol Antimicrob* 13: 41, 2014.
17. Moisei M, Pasarin L, Solomon S, Oanta C, Tatarciuc D, Ursarescu I and Martu S: The role of antibiotherapy in the oral rehabilitation of the periodontal affected patient. *Rom J Oral Rehabil* 7: 107-112, 2015.
18. Vallance S, Jones B, Arabi Y and Keighley MR: Importance of adding neomycin to metronidazole for bowel preparation. *J R Soc Med* 73: 238-240, 1980.
19. Espin-Basany E, Sanchez-Garcia JL, Lopez-Cano M, Lozoya-Trujillo R, Medarde-Ferrer M, Armadans-Gil L, Alemany-Vilches L and Armengol-Carrasco M: Prospective, randomised study on antibiotic prophylaxis in colorectal surgery. Is it really necessary to use oral antibiotics? *Int J Colorectal Dis* 20: 542-546, 2005.
20. Rapone B, Nardi GM, DI Venere D, Pettini F, Grassi FR and Corsalini M: Oral hygiene in patients with oral cancer undergoing chemotherapy and/or radiotherapy after prosthesis rehabilitation: Protocol proposal. *Oral Implantol (Rome)* 9 (Suppl 1/2016 to N 4/2016): S90-S97, 2017.
21. Bonesvoll P and Gjermo P: A comparison between chlorhexidine and some quaternary ammonium compounds with regard to retention, salivary concentration and plaque-inhibiting effect in the human mouth after mouth rinses. *Arch Oral Biol* 23: 289-294, 1978.
22. Dodd MJ, Dibble S, Miaskowski C, Paul S, Cho M, MacPhail L, Greenspan D and Shiba G: A comparison of the affective state and quality of life of chemotherapy patients who do and do not develop chemotherapy-induced oral mucositis. *J Pain Symptom Manage* 21: 498-505, 2001.
23. Nitescu DCK, Constantin M, Oanta C, Martu I, Volovat SR and Martu S: Evaluation of cumulative effects of chemotherapy and bevacizumab (Avastin®) in oncological patients with periodontal disease. *Rev Chim (Bucharest)* 68: 549-552, 2017.
24. Calenic B, Greabu M, Caruntu C, Nicolescu MI, Moraru L, Surdu-Bob CC, Badulescu M, Anghel A, Logofatu C and Boda D: Oral keratinocyte stem cells behavior on diamond like carbon films. *Rom Biotechnol Lett* 21: 11914-11922, 2016.
25. Boda D: Cellomics as integrative omics for cancer. *Curr Proteomics* 10: 237-245, 2013.
26. Neagu M, Constantin C, Tanase C and Boda D: Patented biomarker panels in early detection of cancer. *Recent Pat Biomark* 1: 10-24, 2011.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.