# Evaluation of Cumulative Effects of Chemotherapy and Bevacizumab (Avastin®) in Oncological Patients with Periodontal Disease

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*The aim of this study is to evaluate the periodontal status parameters in patients treated with chemotherapy, with or without the adjuvant bevacizumab, to establish a correlation between the type of administered chemotherapy and periodontal status.*

*Keywords: chemotherapy, bevacizumab, periodontal disease*

Many studies indicate the fact that chronic inflammation and inflammation are linked to the risk of developing cancer [1-3]. Also, there are multiple studies that support the relation between bacterial infections and cercinogenesis [4,5]. Periodontitis leads to cellular proliferation and epithelial migration that results in the release of inflammatory cytokines, prostaglandins, growth factors and enzymes which, in turn, are tightly correlated with malignant tumor development [6].

A history of periodontal disease heightens the risk of developing cancer in comparison to subjects without a history of the disease. It seems that the most significant associations have been established with cancers localized in the lungs, kidney, pancreas and hematological cancers or the maxillo-facial territory[8]. Periodontal disease, in this sense, has been associated with a low but significant risk of cancer with any localization, a fact maintained in non-smokers as well. It seems that the periodontal disease could be a marker for a susceptible immune system as well as a risk factor for cancer.

The use of various types of drugs administered to the complex pathology patient can induse adverse reactions and even more so by combining two or more drugs [9].

Chemotherapy often has an effect of suppression of the immune system. Frequently, in literature, there have been quoted cases of patients treated with chemotherapy agents that developed a series of secondary effects in the oral cavity [10] that lowered their quality of life considerably and lead to the interruption of chemotherapy treatment necessary from the curative or palliative standpoint [11].

Bevacizumab (Avastin®) is part of the anti-angiogenic inhibitors category. In order to take place, angiogenesis require the binding of signaling molecules like the vascular endotelial growth factor (VEGF) to receptors that can usually be found on the surface of endothelium cells. When VEGF and other endothelial growth factors bind to endothelial cell receptors signals are transmitted into their interior where growth and the survival of a new blood vessel is initiated. Angiogenesis inhibitors interfere in many stages of this process [12]. Bevacizumab is a monoclonal antibody that recognizes in a specific manner and binds to VEGF preventing the ladder to activate the receptor [13,14].

Bevacizumab has an ample number of secondary effects that can commonly appear in oncological patients [15]. Among these effects it is worth mentioning gingival hemorrhages, oral inflammations, burning sensations, prickling, pain or numbness in hands and feet, convulsions, cough, extreme fatigue, fever and so on. Hematologically, bevacizumab has as a frequent effect leucopenia and neutropenia, and less frequently, thrombocytopenia [14].

The use of different types of drugs administered to patients may lead to adverse reactions and even more so by combining a higher number of drugs.

Data regarding the frequency of hemorrhagic events, pancitopenia and consecutive severe neutropenia infection remain unclear in scientific literature. The majority of oral secondary effects have their debut a few days (5-7 days) from the administration of the chemotherapeutic agent dose and disappear after 15-20 days. The effects in the oral cavity seems to be directly related to the presence of the chemotherapy agent in the body, the effects ameliorating at the same time with its elimination and along the natural healing process of the body.

## Experimental part
### Materials and method

This study was done on 30 subjects, with ages raging between 44 and 76 years, in the period between november 2014 to november 2015 in the Oncology Clinic of Hospital Victoria, Iasi.

The study respects the norms stated in the Declaration of Helsinki and was done in accordance with the ethics in clinical and paraclinical research principles on human subjects. The patients have been informed regarding the implications of the present study and signed consent was gathered from each individual in order to be included in the research. The study was achieved under the guidance and accord of the Research Ethics Comitee.

In the research we included patients that were diagnosed with systemic cancer, are under chemotherapy and have periodontal disease. In order to avoid the risk of compromising the results, we have considered the following exclusion criteria: smokers, patients with infectious/inflammatory diseases that may affect the

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periodontal status with the exception of systemic cancer, patients that have benefited of periodontal treatment in the last six months or that have followed antibiotic or anti-inflammatory therapy in the last three months.

An observation paper was completed for each individual included in the study that consisted of general data of the patient, oncology and chemotherapy diagnostic data, oral hygiene and periodontal status data. The cancer diagnostic was established by the specialist doctor following clinical and paraclinical examinations.

The oral clinical examination consisted of periodontal history data, dental-periodontal units examination through vertical periodontal probing of the Ramfjord teeth. We have considered pathological depths higher than 3 mm on teeth without gingival recessions.

The indices used were Silness Loe plaque and calculus index, dental mobility index and the periodontal PDI-Ramfjord index.

## Results and discussions

The patients included in the study had systemic cancer localized in the colon (6 cases - 20.0%), esophagus (4 cases - 13.3%), pulmonary (5 cases - 16.6%), rectum (6 cases - 20.0%), kidney (3 cases - 10.0%) and breast (6 cases - 20.0%). From the total of patients, 6 (20%) has stage II cancer, 9 (30%) stage III and 15 (50%) had stage IV cancer.

The oncology treatments that the individuals included in this study benefited of were with the agents zoledronic acid, cisplatin, docetaxel, folfiri (leucovorin + 5-fluorouracil + irinotecan) and oxaliplatin. From the total of 30 patients, 15 had a treatment plan that involved the already named chemotherapy agents and the remaining 15 has a treatment that involved one of the agents in combination with bevacizumab.

**Table 1**
AGE AVERAGE, GENDER AND RESIDENCE DEPENDING ON CHEMOTHERAPY TREATMENT

| Parameter | Non Bevacizumab | Bevacizumab |
|---|---|---|
| Age (average) | 63.93 | 61.00 |
| Gender | 20% B; 80% F | 20% B; 80% F |
| Rural/Urban | 60% U; 40% R | 60% U; 40% R |

40% of patients exhibited high blood pressure besides the cancerous disease, but it could not be established if it represented an entity of its own or as a secondary effect of the chemotherapy.

The mean values regarding age, gender distribution, mean values of the plaque and calculus index and the PDI index were compared in table 1, taking into account the differences between the group that received chemotherapy without the adjuvant bevacizumab and the group that did receive chemotherapy and bevacizumab.

No statistically significant association was found between the mean values of the plaque and calculus index correlated to the administration of bevacizumab, the values being very similar in the two groups taken into account (plaque index 1.886 vs 1.930; calculus index 1.046 vs 1.032).

The mean value of the PDI periodontal index were higher in the group treated with bevacizumab (2.5) compared to the group without bevacizumab treatment (1.74). Value of $p$ was not sufficient in order to give the found values statistical significance.

The mean value of periodontal depth probing also exhibited a difference between the two groups. The mean value of the group that received bevacizumab was higher

| Parameter | Non Bevacizumab | Bevacizumab | *p value* |
|---|---|---|---|
| Mean value of plaque index | 1.886 (0.420) | 1.930 (0.569) | 0.741 |
| Mean value of calculus index | 1.046 (0.619) | 1.032 (0.300) | 0.904 |
| Mean value of PDI index | 1.746 (0.869) | 2.500 (1.513) | 0.121 |
| Mean value of periodontal probing depth | 1.414 (0.313) | 1.837 (0.774) | 0.093 |

**Table 2**
MEAN VALUES DEPENDING ON BEVACIZUMAB ADMINISTRATION

| Non Bevacizumab | Plaque index mean | Calculus index mean | PDI index mean | Periodontal probing depth mean |
|---|---|---|---|---|
| Cisplatin | 1.700 (0.629) | 0.600 (0.522) | 1.650 (1.118) | 1.466 (0.292) |
| Docetaxel | 2.000 (0.200) | 1.200 (0.200) | 1.067 (0.231) | 1.041 (0.115) |
| Oxaliplatin | 2.066 (0.115) | 0.867 (0.115) | 1.667 (0.115) | 1.382 (0.305) |
| Zoledronic acid | 1.963 (0.115) | 1.963 (0.115) | 2.696 (0.115) | 1.713 (0.115) |

**Table 3**
MEAN VALUES OF PERIODONTAL INDEXES EXPRESSED DEPENDING ON THE CHEMOTHERAPY AGENT ADMINISTERED TO THE NON-BEVACIZUMAB GROUP

Table 4

**Table 4**

MEAN VALUES OF PERIODONTAL INDEXES EXPRESSED DEPENDING ON THE CHEMOTHERAPY AGENT ADMINISTERED
IN THE BEVACIZUMAB GROUP

| Bevacizumab | Plaque index mean | Calculus index mean | PDI index mean | Probing depth mean |
|---|---|---|---|---|
| Cisplatin | 1.886 (0.280) | 1.000 (0.200) | 2.800 (0.200) | 1.383 (0.200) |
| Docetaxel | 1.526 (0.115) | 1.330 (0.200) | 1.200 (0.200) | 1.183 (0.200) |
| Oxaliplatin | 2.080 (0.867) | 0.767 (0.175) | 2.700 (2.235) | 2.071 (0.971) |
| Folfiri | 2.267 (0.115) | 1.067 (0.115) | 2.666 (0.115) | 1.716 (0.115) |

| | Plaque $p$ value | Calculus $p$ value | PDI $p$ value | Probing depth $p$ value |
|---|---|---|---|---|
| Cisplatin | 0.543 | 0.371 | 0.191 | 0.789 |
| Oxaliplatin | 0.751 | 0.578 | 0.815 | 0.664 |

**Table 5**

$p$ VALUES BETWEEN PATIENTS TREATED
WITH CISPLATIN AND OXALIPLATIN
VERSUS CISPLATIN AND OXALIPLATIN
AND BEVACIZUMAB

(1.837, standard deviation 0.774) compared to the group that did not include bevacizumab in the treatment (1.414, standard deviation 0.313). For this evaluation, the value of $p$ was 0.093 which signifies weak statistical significance.

Moreover, we have evaluated the relation between the mean values of plaque, calculus and PDI indexes and probing depth taking into account every chemotherapy agent in turn and maintaining the division of the two groups of subjects (bevacizumab and non-bevacizumab) in table 3 and 4, taking into account the possible correlation between them [16-18].

The mean values of the PDI periodontal index in the bevacizumab group were higher than the non-bevacizumab group for patients treated with cisplatin (1.65 vs 2.80; 1.15 difference) and patients treated with oxaliplatin (1.66 vs 2.70, 1.40 difference). The probing depth mean was higher in patients treated with oxaliplatin and bevacizumab compared to individuals treated with oxaliplatin alone (1.38 vs 2.07, 0.69 difference). This difference of probing depth was not seen in patients treated with cisplatin, but a difference was remarked from the calculus index point of view, it having higher values of the mean in subjects treated with cisplatin and bevacizumab (0.60 vs 1.00, 0.4 difference).

Taking into account the secondary effects of oxaliplatin which manifest through neutropenia, neuropathy and thrombocytopenia [19], in combination with bevacizumab which has more secondary effects, it is possible that the general effect on the body is a cumulative one. The values of the percentages quoted in literature vary for each secondary effect in part: neutropenia between 7.8% - 16.3%, neuropathy between 3.9% - 18.4% and thrombocytopenia (6.1%) [20].

The use of various different drugs that are administered to the oncological patient can have diverse reactions and effects, observing that the higher the number of administered drugs, the higher the number of effects.

A weak statistic significance was found nevertheless in patients treated with cisplatin versus cisplatin and bevacizumab concerning the periodontal PDI index.

Lowering the value of this index through treatment can lead to an amelioration of the oral and periodontal secondary effects during chemotherapy [21].

Minimal or lack of oral and periodontal effects of chemotherapy could mean an improvement in the quality of life of cancer patients, a better tolerance of chemotherapy and so a better chance of finishing the entire range of prescribed sessions, the prolonging of life expectancy and an improvement of the psychological status of the patient [4].

**Conclusions**

The present study indicates towards a possible correlation of the chemotherapy agent bevacizumab with an altered periodontal status. The periodontal clinical examination of the subjects in the two groups (with or without bevacizumab) showed differences between the groups. In order to demonstrate the effects of chemotherapy on the evolution of periodontal disease more research is necessary.

**References**
1.ABNET CC, KAMANGAR F, ISLAMI F, NASROLLAHZADEH D, BRENNAN P, AGHCHELI K. Cancer Epidemiol Biomarkers Prev. 2008;17:3062–8.
2.ALLAVENA P, GARLANDA C, BORRELLO MG, SICA A, MANTOVANI A. Curr Opin Genet Dev 2008; 18(1):3-10.
3.ARORA M, WEUVE J, FALL K, PEDERSEN NL, MUCCI LA. Am J Epidemiol. 2010;171:253–9.
4.NITESCU DC, SOLOMON SM, URSARESCU I, MARTU I, MARTU C, MARTU S. Balk J Dent Med, 2015;19:145-149
5.DIVARIS K, OLSHAN AF, SMITH J, BELL ME, WEISSLER MC, FUNKHOUSER WK. Cancer Causes Control. 2010;21:567–75.
6. LUCHIAN ,I, MARTU, I, MARTU, C, GORIUC, A, BELDIMAN, A, MARTU, S. Rev. Chim. (Bucharest), **67**, no. 6, 2016, p. 1073
7.GUJRAL,DM, BHATTACHARYYA, S, MIDDLETON, GW. Journal of Medical Case Reports, 2008;2:47
8.RADULESCU, L, MARTU, C, MARTU, D, DAMEAN, G, COZMA, S. Rom. J. Oral Rehab. 2015;7(1):71-75.
9.MARTU, C, GEORGESCU, MG, MARTU, I, BUTNARU, C, PORUMB, V, RADULESCU, L. Mat. Plast., **53**, no. 2, 2016, p. 321

10.FITZPATRICK SG, KAT J. Journal of Dentistry, 2010; 38:83-95.

11.NITESCU D, SOLOMON S, URSARESCU I, MARTU I, MARTU C, MARTU S. Rom. J. Oral Rehab. 2015; 7(1):101-106.

12.FLETCHER AM, BREGMAN CL, WOICKE J, SALCEDO TW, ZIDELL RH, JANKE HE. Toxicol Pathol. 2010; 38(2): 267-79.

13.HAMERS FPT, GISPEN WH, NEIJT JP. Eur J Cancer, 1991; 27:372-376

14.HONG YS, LEE SS, KIM KP, LEE JL. Am J Clin Oncol. 2014;37(1):19-23.

15.HOLLEY KD., LARCK C, SEHGAL R. Cancer Therapy, 2012; 8:155-158.

16.MEURMAN JH, BASCONES-MARTINEZ A. 2011;17(8):779-784

17.MEYER MS, JOSHIPURA K, GIOVANNUCCI E, MICHAUD DS. Cancer Causes Control. 2008;19:895–907

18.GENCO  RJ., GENCO FD. J Evid Base Dent Pract. 2014;14S: 4-16.

19.TEZAL M, SULLIVAN MA, HYLAND A, MARSHALL JR, STOLER D, REID ME. Cancer Epidemiol Biomarkers Prev. 2009;18:2406–2412

20.TEZUKA T, HAMADA C, ISHIDA H, OOSHIRO M. Invest New Drugs. 2013;31(5):1321-1319

21.TONETTI M, D'AIUTO F, NIBALI L. N Engl J Med. 2007; 356:911-920