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ORIGINAL ARTICLE

Oral status in patients receiving 5-fluorouracil for colorectal cancer

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Summary

Purpose: *Oral complications are frequent and troublesome symptoms for those undergoing chemotherapy for cancer. Several antineoplastic agents are proved to have stomatotoxic potential, among them 5-fluorouracil (5-FU). The aim of the present study was to evaluate the oral status and patient experiences during chemotherapy with 5-FU for colorectal cancer.*

Methods: *Twenty-eight patients treated with 5-day 5-FU plus leucovorin entered this study. Positive data about oral symptoms were taken by anamnesis. Mucositis severity index, gingival index, plaque index, probing pocket depth and bleeding on probing have been used to assess oral mucosa and periodontal status of the patients. Patients were examined prior to chemotherapy and 14 days after the start of the chemotherapy cycle.*

Results: *Mild to moderate subjective complaints concerning oral cavity were reported by 17.9% of patients before and 39.2% of patients after chemotherapy. Clinical examination revealed oral mucosa damage in 10.7% and 35.7% of patients, with mean mucositis score of 0.14 and 0.54 before and after chemotherapy, respectively. Although mean values of all periodontal indices were elevated after chemotherapy, only increase in gingival index was statistically significant (p=0.035). Mucositis was significantly correlated with oral pain (p=0.00), xerostomia (p=0.00), and plaque index (p=0.077), while the correlation between mucositis and the rest of the examined parameters was not significant.*

Conclusion: *Oral complications were not highly expressed in this study. Although 5-FU is considered to exert significant stomatotoxic effect, severe mucositis was far less common in this study compared to studies reported elsewhere.*

Key words: chemotherapy, colorectal cancer, 5-fluorouracil, oral mucositis

Introduction

Patients treated with chemotherapy for different malignancies are often exposed to a number of complications due to compromized immune response, failure of different organs and organic systems, invasive diagnostic procedures and administration of numerous drugs and other therapeutic protocols. It has been documented that about 40% of the patients treated with chemotherapy develop oral complications as well. Damage of the oral mucosa, neutropenia, quantitative or qualitative changes of saliva, altered ratio of different immunoglobulins, especially IgA, and alterations in the composition of oral microflora, are important in the genesis of oral complications in these patients [1,2].

Oral mucositis, which represents the damage that occurs in the mucosal lining of the oral cavity is increasingly recognized as a toxicity associated with many standard-dose chemotherapy regimens commonly used in the treatment of cancer. In its mildest form, it is an enanthematous atrophic lesion in which the mucosa remains intact, while in more severe cases erosions or even ulcerations develop that penetrate fully into the submucosa. Because the mouth harbors a vast array of microorganisms, loss of epithelial integrity, especially in neutropenic patients, significantly increases the risk of bacteremia, fungemia and sepsis. In addition, mucositis adversely affects a variety of other health and economic outcomes. In many patients oral mucositis is associated with considerable pain, which in some cases necessitates even parenteral nutrition and opioid analgesia, and thus can significantly impair the quality of life. Mucositis can also impair the efficacy of chemotherapy in cases where it is necessary to reduce

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the doses of anticancer drugs or to modify the selection of antineoplastic agents. Consequently, this can result in lengthened hospital stay, increased use of resources and higher costs [3,4].

The incidence of oral mucositis varies, depending on the chemotherapy regimen and on different treatment modalities. Approximately 75-85% of bone marrow recipients experience mucositis, and in some studies oral mucositis is the most common and most debilitating side effect reported. Excluding such high-risk regimens, rates of mucositis are generally in the 5-15% range. Several antineoplastic drugs are associated with epithelial toxicity and capability of causing acute apoptosis of the oral mucosa fibroblasts - among them cisplatin, doxorubicin, methotrexate and 5-FU [5].

Methods

Twenty-eight patients (18 male and 10 female, median age 60.8 years, range 47-71) who were about to receive a new cycle of chemotherapy for colorectal cancer at the Institute of Oncology in Sremska Kamenica, Serbia, were enrolled. All of them were treated with the same 5-day schedule of 5-FU 750 mg/m^2/day and leucovorin 25 mg/m^2/day, every 4 weeks. Treatment was given for metastatic or locally advanced disease in 9 patients, and as an adjuvant postoperative therapy in the remaining 19 patients. Twenty-two patients had already received several courses of chemotherapy prior to enrolling to this study, while 6 patients were chemotherapy naïve.

Positive data about subjective oral symptoms were taken by anamnesis. Patients were asked to score the intensity of oral pain, xerostomia, burning mouth sensation and taste alteration according to the following scale:

0 - No symptoms present
1 - Mild discomfort
2 - Moderate discomfort
3 - Severe discomfort

Clinical examination included evaluation of the oral mucosa and periodontal status of the patients. The oral mucosa status was evaluated according to the World Health Organization (WHO) recommendations. Plaque index, gingival index, probing pocket depth and bleeding on probing were used to assess the periodontal status of the patients. The scoring criteria were as follows:

Mucositis severity (WHO):
0 - No efflorescences
1 - Localized erythema of oral mucosa
2 - Diffuse erythema, discrete erosive lesions, can eat solid food
3 - Diffuse erythema, diffuse erosive lesions, ulcerations, liquid diet only
4 - Multiple ulcers, necrosis of oral mucosa, alimentation not possible

Plaque index:
0 - No plaque in the gingival area
1 - A film of plaque that can be detected by probing, but not by inspection
2 - Moderate accumulation of plaque that can be detected by naked eye
3 - Dental plaque in abundance

Gingival index:
0 - Absence of clinically detectable gingival inflammation
1 - Mild inflammation, slight change in color, slight edema
2 - Moderate inflammation, redness, edema and glaze
3 - Severe inflammation, marked redness and edema, ulcerations

Probing pocket depth:

Probing pocket depth was measured with graduated periodontal probe as the distance in mm from the gingival margin to the base of the pocket.

Bleeding on probing:
0 - No bleeding on probing
1 - A single bleeding point at the gingival margin
2 - A fine line of blood or several bleeding points at the gingival margin
3 - Gingival sulcus more or less filled with blood
4 - Profuse bleeding immediately after probing

Each patient was examined and all measurements were taken on two separate occasions: on day 1 of the chemotherapy cycle before drug administration, and 14 days after the start of that chemotherapy cycle.

Statistical analysis

MANOVA, ANOVA, Roy's test and Student's t-test were used to compare the mean values of mucositis severity and mean values of periodontal indices before and after chemotherapy. x^2 test and Cuprov's coefficient were used for establishing the correlation between mucositis, periodontal status and subjective complaints of the patients.

Results

Initial examination revealed presence of oral mucosa lesions in 3 (10.7%) out of 28 patients, manifested as localized or more or less diffuse erythema. Two weeks after the start of chemotherapy, mucositis was registered in 10 (35.7%) patients. Oral lesions were

not only more frequent, but more severe too. Besides erythema, vesicles and discretely or more extensively eroded surfaces were present as well. Mean values of mucositis score before and after chemotherapy were 0.14 and 0.54, respectively (Figure 1).

Periodontal indices achieved rather high values both before and after chemotherapy (Table 1). Although the mean values of all indices were elevated after chemotherapy, only gingival index reached statistically significant level (p=0.035).

Subjective complaints concerning oral cavity were reported by 5 (17.9%) patients before, and 11 (39.2%) patients after chemotherapy, and some of the patients experienced multiple subjective complaints. Most patients (n=9) complained of dry mouth and burning sensation (n=5), while taste alteration (dysgeusia) and oral pain were reported by a minority of the patients (Figure 2). Subjective complaints were more frequently reported after than before chemotherapy, especially xerostomia (p = 0.061) and pain (p = 0.046). With the exception of one patient who described oral pain and xerostomia as being of high intensity, most of the patients graded their subjective complaints as mild or moderate, both before and after chemotherapy.

Mucositis was significantly correlated with oral pain (p= 0.000), xerostomia (p= 0.000) and plaque index (p= 0.077), while the correlation between mucositis and the rest of the examined parameters was not significant (Table 2).

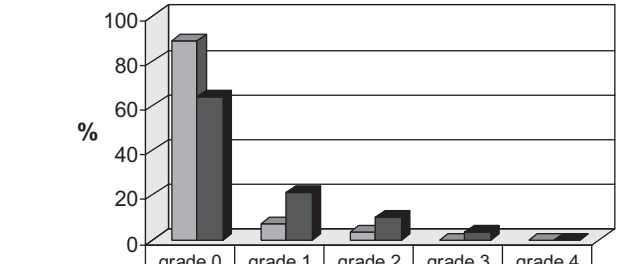

Figure 1. Mucositis severity. Columns represent the percentage of patients with mucositis of each WHO grade before and after chemotherapy.

Table 1. Periodontal status before and after chemotherapy

	Before chemo	*After chemo*	*p-value*
Plaque index	1.65±0.28	1.72±0.31	0.199
Gingival index	1.51±0.20	1.65±0.24	0.035
Pocket depth	4.20±1.28	4.36±1.25	0.621
Bleeding index	1.32±0.26	1.39±0.22	0.261

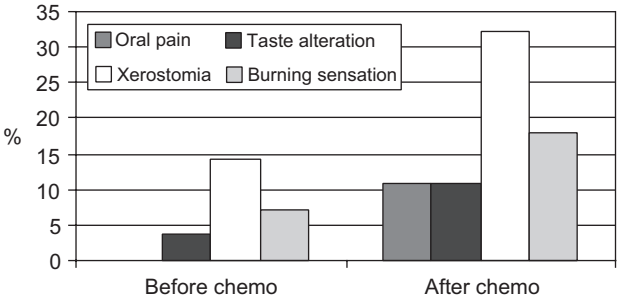

Figure 2. Subjective difficulties. Columns represent the percentage of patients with each subjective difficulty before and after chemotherapy.

Table 2. Correlation between mucositis, subjective difficulties and periodontal status

	x^2	*T*	*p-value*
Xerostomia	78.919	0.597	0.000
Burning sensation	10.227	0.238	0.249
Oral pain	89.424	0.635	0.000
Taste alteration	9.524	0.229	0.300
Plaque index	14.158	0.280	0.077
Gingival index	10.209	0.237	0.251
Bleeding index	16.837	0.276	0.156

Discussion

In the relevant literature, one can find that an average of 40% of patients treated with chemotherapy experience oral mucosa damage. The range of patients having oral changes is rather wide - from 13 to 80%, depending on the nature of the existing malignancy and on the therapeutic protocol applied [6]. A considerable number of studies deals with the type of education of the examiner: when it is other than dentistry, mild oral changes are usually not detected [7]. Differences in results of different studies could also be attributed to different scoring systems which may show presence of mucositis ranging from 30 to 69% in the same group of patients [8]. Owing to these reasons the results of studies on oral mucositis can not be always compared with reliability.

5-FU is one of the agents known for causing mucositis. Data shows that administration of 5-FU, with or without leucovorin, is associated with oral mucositis in as much as 40% of the patients, while grade 3-4 mucositis approaches 10-15% [5]. Some researchers report even 30% of grade 3 or more mucositis in 5-FU recipients [9,10]. In this study, oral mucositis was found in 10.7% of patients before and 35.7% of patients after chemotherapy, which is close to the findings we have previously reported [11]. Mucositis was mostly in the form of erythema and erosions of the oral mucosa, with differ-

ent combinations and severity. The mean value of mucositis score was rather low - 0.14 before and 0.54 after chemotherapy. More severe mucositis was less common in our study than in other studies, with only 1 (3.6%) patient with grade 3 and no patients with grade 4 mucositis. Explanations for such results can be numerous. None of the patients in the present study was severely myelosuppressed with absolute neutrophil count never less than 1500 cells/ml, while neutropenia is known to be one of the most important risk factors for the development of mucositis. Another possible explanation could be the rather older age of our patients. Data show that among patients with the same malignancy, and treated in the same way, mucositis is more frequently detected in younger individuals [12]. But the most convincing explanation for poor oral findings in our study can probably be due to the fact that none of our patients was hospitalized, but admitted to the hospital just to receive chemotherapy. With no opportunity of seeing those patients on a daily basis, it is more than likely that some cases of mucositis went unregistered. Although it is difficult to predict which patients will develop oral complications, data show that the direct stomatotoxic effect is closely related to the dose of drug in question. On the other hand, patients themselves express different levels of tolerance to antineoplastic agents. The same dose of drug will be stomatotoxic in one patient and not in the other. It was also found that the risk of developing mucositis increases with the number of chemotherapeutic cycles, and that patients who experienced oral changes during one cycle of chemotherapy, also experienced them during the following cycles, with similar localization and intensity [13]. However, the present study showed that the incidence of mucositis was higher during the first than during the subsequent cycles. Three out of 6 (50%) chemotherapy naïve patients experienced oral mucositis during their first cycle of therapy. This, in our opinion, can be explained by the additional immunosuppression caused by complicated and aggressive diagnostic procedures preceding therapy.

The periodontal status of patients undergoing chemotherapy is not usually considered as important. But, as the most of adult population is suffering from periodontal disease, it should be kept in mind that periodontal pockets can be a reservoir of infection and a potential source for systemic spread of infection and bacteremia. Ulcerations and necrosis of proliferated sulcular and junctional epithelium, that persist and can not be clinically detected may facilitate spread of the infection into the underlying tissues. During neutropenia, even acute exacerbations of periodontal infection may frequently be overlooked [14,15]. The results obtained in this study show increase in periodontal inflammation during chemotherapy. This particularly refers to the gingival index which was significantly elevated. The intensity of gingivitis is usually dependent on the amount of tooth deposits and poor oral hygiene. However, literature data indicate that in these patients gingival inflammation may develop even if oral hygiene is appropriate [16]. The results of this study also indicate significant increase in the gingival index, despite only moderate increase in the plaque index values. This finding could be an additional indicator that pathological processes in periodontal tissues in patients undergoing chemotherapy are not only influenced by the presence of dental plaque but also by impaired immunity, particularly by altered IgG/IgA ratio in the saliva [17,18].

Subjective complaints were not highly expressed and most of the patients described them as mild or moderate. With the exception of pain, patient experiences of oral symptoms during chemotherapy are rarely reported and the literature data on this topic differ substantially. This might be explained by differences in the psychological structure of the participating patients, the kind of malignancy, treatment regimen and the time of symptoms registration. Registering subjective complaints on a daily basis is particularly important for mild symptoms, which are, after a period, neglected by the patients [19]. We believe that this might be the reason for the rarity of reporting subjective complaints in our study, in which participants were asked about this matter two weeks after starting chemotherapy. Another possible explanation might be that patients in poor condition report mouth pain and dryness less frequently than they actually exist, probably because they are more concerned about other problems created by their disease [20]. Oral pain and dysgeusia can lead to loss of appetite, impaired food intake and loss of body weight which can additionally increase susceptibility to infection. Malnutrition may also interfere with pharmacokinetics and drug metabolism by increasing their toxicity. All these, at the end, may result in unsatisfactory therapeutic response [21,22].

Although oral complications were not as common and severe in our study as reported elsewhere, they create a troublesome situation for those undergoing chemotherapy. It is well documented that the oral cavity might serve as gate of entry for systemic spread of infections and septicaemia. In addition, oral symptoms may lead to discouragement, depression, anorexia, and physical weakness. It is easily understood that such a scenario could affect the continuation of cancer treatment. Therefore, oral status of patients undergoing chemotherapy must be taken into serious consideration. Strategies for minimizing oral complications may improve the quality of life of these patients and be beneficial for the success of treatment of malignant diseases.

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