CORRELATIONS BETWEEN THE CLINICAL STATUS OF ORAL MUCOSA AND THE DYNAMICS OF PERIPHERAL BLOOD NEUTROPHILS IN CHILDREN WITH CHEMOTHERAPY-INDUCED NEUTROPENIA

Katarzyna Olszewska,

Maria Mielnik-Błaszczak, Artur Michałowski

Chair and Department of Developmental Age Stomatology, Medical University of Lublin

Abstract

Introduction. Mucositis is the most common complication of chemotherapy observed within the oral cavity. As a consequence of myeloablative chemotherapy, mucositis affects about 30-70% of patients receiving cytostatic drugs and about 60-100% of patients undergoing stem cell transplants. The term "mucositis" refers to oral mucosal lesions consisting in oral epithelium being damaged as the result of chemo- or radiotherapy.

Aim. The objective of the study was to assess the potential correlations between the clinical status of oral mucosa and the dynamics of peripheral blood neutrophils in children with neutropenia due to anticancer treatment.

Material and methods. The study was conducted in a group of 52 children aged 3-17.5 years, diagnosed with cancer and undergoing treatment at the Department of Paediatric Haematology and Oncology and Transplantology. The study group consisted of 22 girls and 30 boys. The mean age was 7.83 years.

Results. Statistical analysis using the Kendall's tau correlation test revealed a negative correlation between the blood neutrophil counts (NEU) and WHO grade of oral mucositis in test 1 (T1) (Z=-4.2571; p=0.0001), test 2 (T2) (Z=-7.2546; p=0.0001), and test 3 (T3) (Z=-4.9360; p=0.0001). In patients with reduced blood neutrophil counts, an increased severity of oral mucositis-type lesions was observed.

Conclusions. The intensity of oral lesions reaches its maximum levels at the time the neutrophil counts within peripheral blood are the lowest. Lesions resolve, as neutrophil counts are increased again. The intensity of oral lesions is, thus, a reflection of the intensity of neutropenia.

Key words: chemotherapy, neutropenia, mucositis, oral cavity, children.

Introduction

After poisonings, trauma and accidents, malignancies are the second most common cause of death of children aged 1 year and over [1]. Currently, a large number of childhood cancers are considered curable; for most of them, the recovery rates exceed 80%, while some types are curable in as much as 98% of cases. In nearly all types of childhood cancers, complete recovery, i.e. permanent elimination of all cancer cells

from the system, became possible only after introduction of chemotherapy. The toxicity of chemotherapeutic regiments and drug resistance are responsible for limitations to the applicability of this treatment. Due to the antiproliferative mechanism of cytotoxic agents, tissues and organs characterized by the highest rates of cell divisions (bone marrow, mucosal membranes within the respiratory and gastrointestinal tract, skin, hair, and gonads) are at the highest risk of toxic effects of therapeutic regimens. Cytostatic drugs are responsible for neutropenia, which is the most important factor promoting the development of infections. The risk of infection is significantly increased for total neutrophil counts lower than 1000/mm^3, and particularly increased for neutropenia of less than 500/mm^3 [2]. Mucositis is the most common complication of chemotherapy observed within the oral cavity. As a consequence of myeloablative chemotherapy, mucositis affects about 30-70% of patients receiving cytostatic drugs and about 60-100% of patients undergoing stem cell transplants. The term "mucositis" refers to oral mucosal lesions consisting in oral epithelium being damaged as the result of chemo- or radiotherapy. The intensity of oral lesions reaches its maximum levels at the time the neutrophil counts within peripheral blood are the lowest. Lesions resolve as neutrophil counts are increased again [3].

Aim

The objective of the study was to assess the potential correlations between the clinical status of oral mucosa and the dynamics of peripheral blood neutrophils in children with neutropenia due to anticancer treatment.

Material and methods

The study was conducted in a group of 52 children aged 3-17.5 years, diagnosed with cancer and undergoing treatment at the Department of Paediatric Haematology and Oncology and Transplantology. The study group consisted of 22 girls and 30 boys. The mean age was 7.83 years. The study had received the approval of the Bioethics Committee at the Medical University of Lublin (resolution no. KE-0254/217/2011).

Children undergoing anticancer treatment were examined three times during their hospitalization stays. First test was performed within the first 7 days after initiation of chemotherapy cycle (T1), the second test was performed within 7-21 days after initiation of chemotherapy cycle (T2), while the third test was performed within 21-30 days after initiation of chemotherapy cycle (T3). Control group subjects were examined only once.

Neutropenia was diagnosed as neutrophil counts of <1500/μL and classified as follows:
– Mild neutropenia (granulocyte counts of 1-1.5×103/μL),
– Moderate neutropenia (granulocyte counts of 0.5-1×103/μL),
– Severe neutropenia (granulocyte counts of <0.5×103/μL),
– Life-threatening neutropenia (granulocyte counts of <0.1×103/μL).

Clinical examination of oral cavity was performed in artificial lighting using a dental mirror and explorer probe. Mucosal assessment included evaluation of mucosal

color, hydration, and presence of pathological lesions such as erythema, edema, erosions, ulcerations, blisters, ecchymosis, petechiae, and deposits. Areas subjected to examination included lips, buccal cavity, tongue, mouth floor, cheeks and palate.

Clinical examination involved the screening of oral mucosa for mucositis-type lesions. Mucositis type lesions were clinically characterized using the five-point WHO scale:

0 – no pathological lesions in oral mucosa;

1 – redness, erythematous lesions with accompanying pain;

2 – erythematous lesions, erosions, pain, patient able to eat solid food;

3 – extensive erythema, strong pain, patient requires liquid diet, unable to eat solid food;

4 – severe inflammation symptoms; patient unable to receive food by mouth, requires parenteral nutrition.

Statistical analysis

The obtained results were submitted to statistical analysis using STATISTICA 10 software. Kendall's tau coefficient of correlation was used to measure correlation between blood neutrophils count and oral mucositis incidence and severity. A five-percent margin of error was assumed, and therefore significance level of $p < 0.05$ was considered to indicate statistical significance. Statistically significant differences were marked with an *.

Results

Peripheral blood neutrophil counts (NEU) were monitored in study group patients in the course of anticancer treatment. Statistically significant differences were observed between neutrophil counts in test 1 (T1), test 2 (T2), and 3 (T3) (Friedman's ANOVA=56.42; p=0.001). The highest counts of peripheral blood neutrophils were observed for T1, i.e. within the first 7 days from the start of the chemotherapeutic cycle (M=5.057; SD=5.63), while the lowest counts were observed for T2, i.e. 7-14 days from the start of the chemotherapeutic cycle (M=0.71; SD=0.45). The largest and the lowest percentages of neutrophils (NEU) in leukocyte (WBC) differential tests were observed for test 1 (M=40.84; SD=30.52) and test 2 (M=23.53; SD=16.29), respectively.

Grade 2 and 3 oral mucositis-type lesions were most common in children with severe neutropenia ($<0.5\times10^3/\mu L$), grade 2 lesions were most common in children with moderate neutropenia ($0.5\text{-}1.0\times10^3/\mu L$), and grade 1 lesions were most common in children with mild neutropenia ($1.0\text{-}1.5\times10^3/\mu L$). Detailed data on the incidence of oral mucositis in relation to the severity of neutropenia in test 1 (T1), 2 (T2) and 3 (T3) are presented in Tables 1, 2 and 3.

Statistical analysis using the Kendall's tau correlation test revealed a negative correlation between the blood neutrophil counts (NEU) and WHO grade of oral mucositis in test 1 (T1) (Z=-4.2571; p=0.0001), test 2 (T2) (Z=-7.2546; p=0.0001), and test 3 (T3) (Z=-4.9360; p=0.0001). In patients with reduced blood neutrophil

counts, there observed increased severity of oral mucositis-type lesions. The results of statistical analyses are presented in Figures 1, 2 and 3.

Table 1. Incidence of oral mucositis in relation to the severity of neutropenia in test 1 (T1)

Neutropenia	Oral mucositis WHO classification									
	0		I°		II°		III°		IV°	
	n	%	n	%	n	%	n	%	n	%
mild	10	90.91	1	9.09	0	0	0	0	0	0
moderate	6	54.55	4	36.36	1	9.09	0	0	0	0
severe	1	25.00	3	75.00	0	0	0	0	0	0
life-threatening	0	0	0	0	0	0	0	0	0	0

Kendall's tau=0.4579; Z=3.2803; p=0.001*
Z – statistical analysis, test function value, U Mann-Whitney test
p – level of significance

Table 2. Incidence of oral mucositis in relation to the severity of neutropenia in test 2 (T2)

Neutropenia	Oral mucositis WHO classification									
	0		I°		II°		III°		IV°	
	n	%	n	%	n	%	n	%	n	%
mild	17	100	0	0	0	0	0	0	0	0
moderate	8	61.54	1	7.69	4	30.77	0	0	0	0
severe	2	11.11	1	5.56	11	61.11	4	22.22	0	0
life-threatening	0	0	1	25.0	0	0	3	75.0	0	0

Kendall's tau=0.714996; Z=7.481405; p=0.0001*
Z – statistical analysis, test function value, U Mann-Whitney test
p – level of significance

Table 3. Incidence of oral mucositis in relation to the severity of neutropenia in test 3 (T3)

| Neutropenia	Oral mucositis WHO classification									
	0		I°		II°		III°		IV°	
	n	%	n	%	n	%	n	%	n	%
mild	14	66.67	7	33.33	0	0	0	0	0	0
moderate	4	25	10	62.5	2	12.5	0	0	0	0
severe	1	33.33	0	0	2	66.67	0	0	0	0
life-threatening	0	0	0	0	0	0	0	0	0	0

Kendall's tau=0.44867; Z=4.077564; p=0.0001*
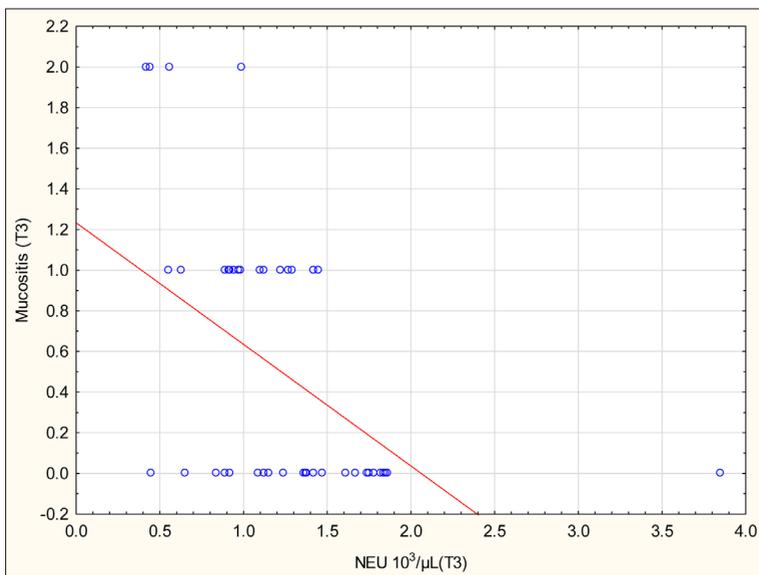Z – statistical analysis, test function value, U Mann-Whitney test
p – level of significance
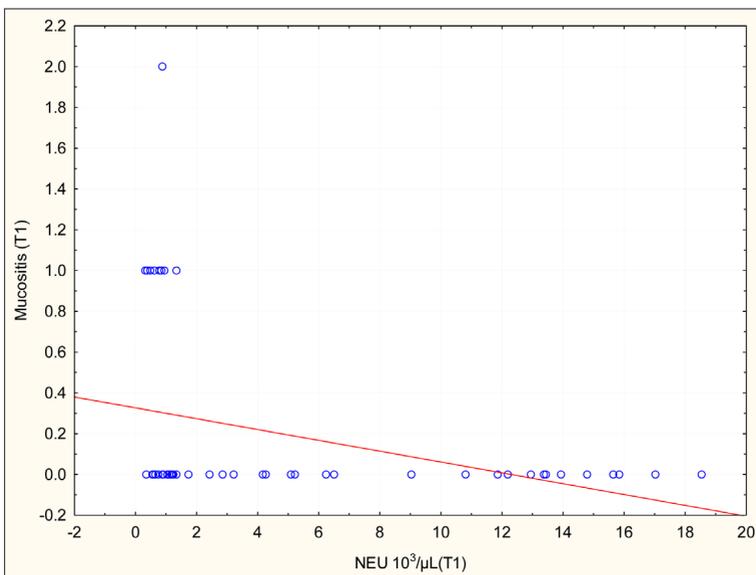
Figure 1. Correlation between blood neutrophil count (NEU) and oral mucositis in test 1 (T1)
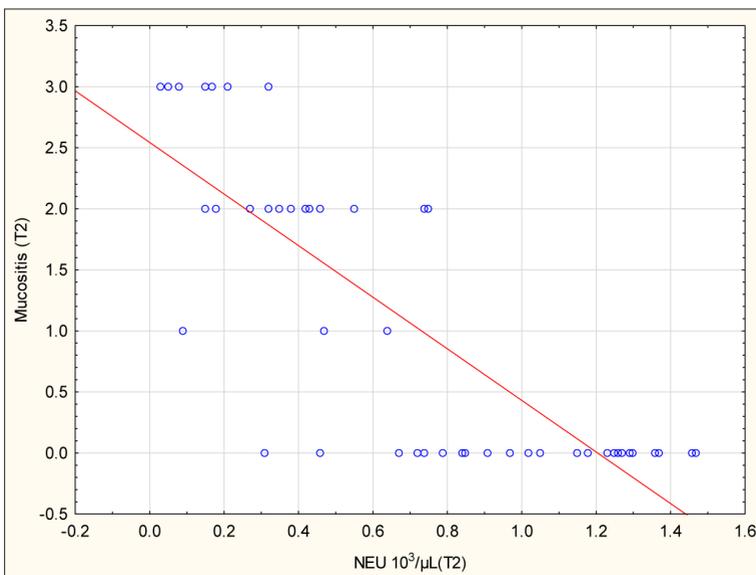
Figure 2. Correlation between blood neutrophil count (NEU) and oral mucositis in test 2 (T2)

Figure 3. Correlation between blood neutrophil count (NEU) and oral mucositis in test 3 (T3)

Discussion

Mucositis is the most common complication of cytotoxic anticancer treatment observed within the oral cavity. High risk group consists in patients prepared for bone marrow transplants, patients undergoing whole body irradiation or induction of anti-leukemia treatment, and patients with head and neck cancers. The risk of mucositis is also significantly increased by mucosal injuries, secondary infections, and xerostomia [4,5].

In line with numerous literature reports, mucositis increases the risk of bacteremia and systemic infections, extends hospitalization times and increases treatment costs while reducing the quality of life of cancer patients [6]. Studies on bacteremia in cancer patients revealed that the risk of sepsis in neutropenic patients with oral mucositis-type lesions is four times higher than that in neutropenic patients without mucositis-type lesions [7]. According to the literature data, 38% of patients undergoing radiotherapy and 42% of patients receiving intensive multiagent chemotherapy considered mucositis to be the worst side effect of their cancer treatment [8].

Mucositis-type lesions usually persist within the oral cavity for about 3 weeks. They develop within 3-5 days from the start of chemotherapeutic cycle and reach their peak intensity between therapy days 7 and 14, as confirmed in our own study. Later on, lesions resolve, provided no secondary infection has developed. Studies by numerous authors also showed that the severity of mucositis-type lesions is strongly correlated with the degree of myelosuppression, with the most severe mucositis-type lesions being

observed within the oral cavity during the largest drop in blood neutrophil counts [9-11]. This was confirmed in this study where a significant correlation was detected between the peripheral blood neutrophil counts and the incidence and severity of oral mucositis-type lesions. According to Sonis [3], the most severe mucositis-type lesions are observed 3-4 days before neutropenic nadir, which is usually achieved about 14 days after the start of chemotherapy. In our own study, the highest severity of oral mucositis-type lesions was observed between day 7 and day 21 from the initiation of chemotherapy cycle.

In our own studies, mucositis was observed in 48.08% of studied paediatric patients presenting with neutropenia in the course of intensive multiagent chemotherapy. According to Filicko *et al.* [12], mucositis develops in 90-100% of patients subjected to aggressive myelosuppressive chemotherapy. In the studies by Elting *et al.* [6], mucositis-type lesions were observed within the oral cavities of 51% of patients receiving chemotherapy for solid tumors or lymphomas. According to Sonis and Fey [4], about 8% of cancer patients are at high risk of developing ulcerative mucositis during anticancer treatment, whereas 43% of patients are in the low risk or no risk group.

In the study by Karolewska *et al.* [13] conducted in a group of paediatric patients with leukemia, mucosal lesions were observed in 75% of subjects. The highest percentage of lesions were mucositis-type lesions developing as a side effect of cytostatic drugs (41.25%) . Pels [14] observed oral mucosal erythema in 35% of studied paediatric patients with ALL. Anirudhan *et al.* [15] carried out a study of the etiology of mucositis in a group of paediatric acute lymfoblastic leucemia (ALL) patients aged 6 months to 15 years (mean age of 4.25), treated according to the MCP-841 protocol and presenting with oral mucosal lesions. Overall, a total of 100 mucositis episodes were recorded in 70 patients. The highest number of mucositis episodes was observed during the cancer treatment induction phase. The most common mucosal lesions included ulcers (70%) followed by spots (18%) and blisters (3). Most prevalent pathogens isolated from mucosal lesions included fungi (38 cases), followed by bacteria (23 cases). WHO grade 1 mucositis was observed in 37% of patients; grade 2 mucositis was observed in 30% of patients, grade 3 mucositis was observed in 23% of patients, and grade 4 mucositis was observed in 10% of patients. Neutropenia was observed in 64% of mucositis cases, including in 61.2% of paediatric patients with mild mucositis (WHO grade 1 or 2) and in 69.7% of patients with severe mucositis (WHO grade 3 or 4). In our own study, grade 2 and 3 mucositis-type lesions were most common in children with severe neutropenia (<0.5×10³/μL), grade 2 lesions were most common in children with moderate neutropenia (0.5-1.0×10³/μL), and grade 1 lesions were most common in children with mild neutropenia (1.0-1.5×10³/μL).

Konopka *et al.* [16] examined the condition of oral cavity in 31 paediatric leukemia patients aged from 3 to 18 years and undergoing anticancer treatment. In acute lymphoblastic leukemia (ALL), WHO grade 2 lesions and exfoliative cheilitis were most commonly observed, while gingival hyperplasia was most common in acute non-lymphoblastic leukemia (ANLL). Although mucosal lesions were observed

in more than 48% of patients, the most common diagnosis included coated tongue. Grade 2 mucositis-type lesions were observed only in ALL patients, while grade 1 and 2 lesions were diagnosed in ALL and ANLL.

Grzegorczyk-Jaźwińska *et al*. [17] assessed the condition of oral mucosa and periodontium in 31 adult patients before and after hematopoietic stem cell transplant. Grade 1 mucositis was observed in 45% of patients. Grade 2 mucositis was observed in 1 patient after allogeneic transplant, while grade 3 mucositis was observed in 2 patients. The highest intensity of mucositis was observed between day 7 and day 14 following the transplant.

Conclusions

The results of the study revealed a significant correlation between the peripheral blood neutrophil counts and the incidence and severity of oral mucositis lesions. The intensity of oral lesions reaches its maximum levels at the time the neutrophil counts within peripheral blood art the lowest. Lesions resolve, as neutrophil counts are increased again. The intensity of oral lesions is, thus, a reflection of the intensity of neutropenia.

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Address for correspondence
Katarzyna Olszewska
Chair and Department of Developmental Age Stomatology
Karmelicka St. 7, 20-081 Lublin
E-mail: olszewskakm@interia.pl

ASSESSMENT OF THE ORTHODONTIC TREATMENT NEEDS IN THE LUBLIN VOIVODESHIP RESIDENTS

Marzena Pucek[1], Beata Kubić-Filiks[2], Jolanta Szymańska[2]

[1] Beautiful Smile Clinic, Lublin
[2] Department of Integrated Paediatric Dentistry, Medical University of Lublin

Abstract

Introduction. When a patient reports to an orthodontist, it does not always mean a necessity of beginning the treatment. Therefore, the demand for treatment – patient's willingness to be treated is not equal to a need for treatment. Conducting professional evaluation of occlusion made by a specialist/specialists on the basis of thorough objective examination allows to either confirm or exclude the need for orthodontic treatment.

Aim. Assessment of the orthodontic treatment needs among the population residing in the Lublin Voivodeship.

Material and methods. Retrospective analysis of medical documentation from the years 2015-2016 was made in two dental offices from the Lublin Voivodeship, in which professional orthodontic treatment was offered; one dental office is located in a big urban centre – Lublin, and one in a small city – Łuków. Orthodontic treatment was required in 1609 patients, who were divided into three age groups for the analysis purpose: 6-12 years old (Group I), 13-19 years old (Group II) and 20 years old or above (Group III). Collected data were statistically analysed.

Results. An analysis of the medical documentation (a year after year comparison) showed an increase in the orthodontic treatment needs by 14.96% in the big city and by 83% in the small city. The increase in orthodontic treatment needs especially concerned the population of children up to 12 years old, followed by persons over 20 years old and the youth in the age 13-19 years old. The biggest orthodontic treatment needs were found in the mean age of 13.2 years.

Conclusions.
1. Significant increase in orthodontic treatment needs in the Lublin Voivodeship residents is observed.
2. It is reasonable to verify the age criteria concerning reimbursement of orthodontic treatment by the National Health Fund, taking into consideration 13-year-olds.

Keywords: malocclusions, treatment needs, children, youth, adults.

Introduction

National epidemiological studies concerning state of oral health conducted in Poland during the last 17 years have shown approximately 54% rate of occlusal disorders in children and youth who are eligible for orthodontic treatment, what gives evidence of great orthodontic treatment needs in the population of the young Poles.