Assessment of salivary flow rate and secretory immunoglobulin A and oral mucosal changes in acute myeloid leukemia before and after the induction phase of chemotherapy

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ABSTRACT
Background: Acute myeloid leukemia (AML) is a hematological disorder characterized by the presence of immature hematopoietic cells in the bone marrow and blood. These malignant cells do not differentiate normally, and thus may block the differentiation of the remaining normal hematopoietic precursors. Chemotherapy is the treatment of choice of AML. The aim of the study was to determine the salivary flow rate and the S-IgA secretion rate in AML patients before and after chemotherapy and to assess oral mucositis after chemotherapy and to report any other oral mucosal manifestations.

Materials and Methods: A total of 40 patients just diagnosed as having acute myeloid leukemia participated in the study. The control group consisted of 20 healthy subjects. Clinical oral examination took place at the time of the diagnosis, and again one month following chemotherapy.

Results: The most serious oral complication is the mucositis which developed in (52.5%) of AML patients after chemotherapy. Before chemotherapy the salivary flow rate and S-IgA secretion rate were significantly lower than their values in healthy subjects (p<0.001 and p<0.007), after chemotherapy, a further reduction in their values was detected. AML patients with oral mucositis presented with lower S-IgA level compared with their counterparts with no mucositis (p<0.02).

Conclusion: Oral mucositis is a common and serious problem during chemotherapy. The salivary flow rate and S-IgA levels are significantly reduced in AML patients undergoing chemotherapy which in turn affect general oral health status.

Keyword: Acute myeloid leukemia, chemotherapy, mucositis, salivary S-IgA.

INTRODUCTION
Acute myeloid leukemias (AMLs) comprise a heterogeneous group of diseases characterized by infiltration of the blood, bone marrow, and other tissues by neoplastic myeloid cells of the hematopoietic system (1).

Oral complications of leukemia frequently include gingival hypertrophy, petechiae, ecchymosis, mucosal ulcers, and gingival hemorrhage (2).

Acute myeloid leukemic patient was usually treated with combination chemotherapy, includes daunorubicin and cytarabine, the mechanism of action of chemotherapeutical agents is based on an inhibition of cellular processes, especially those related to the nucleic acid metabolism, which inactivates the cell mitosis. Selective chemotherapy targeted against selected organs is currently not possible (3,4).

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difficulties in maintaining such functions. Furthermore, deterioration of oral health and distressing oral symptoms including dry mouth have been shown to have a significant influence on cancer patients' experience of overall quality of life both during and after treatment (7).  

Salivary immune factors are represented mainly by immunoglobulins, of which Immunoglobulin A (IgA) is the key immunoglobulin in mucosal immunity. IgA is present also in serum and other body secretions like milk, jejunal fluid, hepatic bile and tears (8). S-IgA originates purely from salivary glands, which mainly acts to inhibit adherence of bacteria to tooth and oral mucosal surfaces and may assist in phagocytosis of bacteria by neutrophils. It also acts by neutralization of enzymes, toxins, and viruses. It interacts with nonspecific antibacterial factors like lactoferrin, lysozyme and peroxidases, so when the level of salivary S-IgA decreased this will be associated with increased risk for periodontal disease and caries (9).  

Several studies revealed that the concentrations of S-IgA in saliva were significantly decreased during treatment with chemotherapeutic agents, because chemotherapy causes a systemic immunosuppression with severe depression of the bone marrow (4).

**MATERIALS AND METHODS**

**Materials**

The materials used in this study: Salivary S-IgA indirect enzyme immunoassay kit (Catalog No. 1-1602, 96 well kit, for research use), Salimetrics, USA and Canada

**Patients Group**

Forty patients (18 males and 22 females), just diagnosed as having acute myeloid leukemia, admitted to Baghdad Teaching Hospital and Hematology Center in Al-Yarmok Teaching Hospital, in Baghdad city, were studied as patients group, throughout the period between January to July 2008. The diagnosis was established by bone marrow aspiration and biopsy carried out by specialists in those centers. Criteria proposed by (FAB) group were applied to classify the cases. Full medical history and general physical examination were done for each patient by expert physicians to exclude any existing evidence of systemic disease that may affect S-IgA level in saliva such as diabetes mellitus, autoimmune disease, upper respiratory tract infections and salivary gland diseases.

**Control Group**

Twenty non-hospitalized subjects (9 males and 11 females), with negative medical history and not on any medication, who exhibited no oral lesions, with age and gender distribution compatible with those of the patients group, were taken as control group for the study.

Subjects with periodontal diseases and/or those who had undertaken major dental work were excluded from both groups; the exclusion was based on results of oral examination carried out by one of the researchers, to avoid any effect on S-IgA levels.

**Oral Examination**

All patients were examined in bed using a portable light and disposable dental mirror. Lips, mucosa, tongue, palate and gingivae were examined for the presence of any oral lesions.

The oral examination took place at the time of the diagnosis of leukemia (as soon as possible after admission to hospital), to determine any oral manifestations related to acute myeloid leukemia. Then they were re-examined one month after starting chemotherapy to evaluate mucositis and other oral manifestations related to chemotherapy treatment.

The presence of mucositis was coded according to the World Health Organization's (WHO) grading system; one of the most commonly used systems, especially in clinical studies. The criteria for grading the severity of mucositis were as follows: (11).

1. Localized erythema of oral mucosa.
2. Diffuse erythema, discrete erosive lesions, patient can eat solid food.
3. Diffuse erythema, diffuse erosive lesions, ulceration, patient requires liquid diet only.
4. Multiple painful ulcers, necrosis of oral mucosa, oral alimentation is not possible; patient requires parenteral support or opiate analgesic.

**Saliva Collection**

Two samples of saliva were collected from each patient and one sample from each member of the control group, first salivary sample was taken from each AML patient before receiving cytotoxic chemotherapy (induction phase), while the second salivary sample was taken 3 weeks after the end of induction phase of chemotherapy.

Unstimulated mixed (resting) saliva was collected by seating the patient comfortably with open eyes. Saliva was allowed to flow for 5 minutes period by the patient leaning forward and letting it drain into pre-weighed plane tube. All saliva samples were collected between 9.00 and 11.00 A.M to negate the influence of diurnal variation of saliva constituent (12, 13). To minimize the potential of saliva contamination particularly from dairy products, both patients and control group members were requested to refrain from drinking, eating, smoking and oral hygiene activities for a minimum of 2 hours before saliva collection.
procedures at least one hour preceding the collection of the saliva samples \(^{(14)}\). Acidic or high sugar foods can compromise assay performance by lowering sample pH and influencing bacterial growth. To minimize these factors, participants were asked to rinse their mouth thoroughly with tap water 10 minutes prior to sample collection. It was also decided that samples visibly contaminated with blood should be recollected.

After collection of saliva samples, it was advised to keep the samples cold, in order to avoid bacterial growth in the specimen. Samples were refrigerated within 30 minutes, and frozen at or below -20ºC within 4 hours from collection to precipitate the mucins. On day of assay, they were thawed completely in room temperature, vortexed, and centrifuged at 3000 rpm for 15 minutes.

The flow rate of saliva was estimated by dividing the saliva sample volume (ml) by the collection time (min) that measured during sample collection \(^{(15)}\). A highly sensitive digital balance was used for weight measurement, then the weight of saliva sample was determined by weighing the tube before and after collection, then the weight of each saliva sample (g) was equated to the volume (ml), since the specific gravity of saliva is 1.0 \(^{(16)}\).

**RESULTS**

Following analysis of data related to age and gender of patients group, it was found that out of 40 AML patients; 18 (45%) patients were males and 22 (55%) patients were females. Patients age ranging from 16 to 77 years, with mean age of (40.61 ± 21.34) years for male patients and (33.14 ± 16.26) years for female patients were included in this study. Distribution of age and gender of the AML patients is presented in table 1. Statistically there was no significant difference between male and female distribution.

**Oral finding**

Clinical examination showed that hemorrhage is the most prevailing finding in AML patients before and after chemotherapy (42.5% and 52.5% respectively).

Second most common finding is oral infections which covers candidal thrush, angular cheilitis, and herpes labialis, while black hairy tongue maintained the least number of cases before and after chemotherapy contributed in (5% and 12.5% respectively) AML patients only. Statistically only gingival enlargement and mucositis were significantly different before and after chemotherapy (P<0.003 and P<0.000001 respectively) as shown in table 2.

One of the prime aims of this study is to highlight the development of oral mucositis in patients with AML following chemotherapy. Interestingly none of the patients showed mucositis before treatment, whereas following chemotherapy oral mucositis was developed in more than half of the patients and precisely in 21 cases. The patients complain from various grades of mucositis. The majority of patients showed grade 1 and 2 (17 cases), whereas only four patients developed grade 3 and 4 mucositis as shown in figure 1.

Still out of the 40 AML patients, 19 of them (47.5%) have had no mucositis (grade 0) after chemotherapy while 52.5% of patients with AML complained from various grades of mucositis, statistically, there were no significant gender differences in the tendency to develop mucositis after chemotherapy.

In this study, the incidence of mucositis decreases among older age groups, (38% of the cases were among 15–25 years old). Statistically this correlation is not significant (r=-0.16, P=NS).

Salivary flow rate was found to be inversely correlated with the age of healthy subjects. These relationships were maintained in patients with AML weather before chemotherapy or after chemotherapy, although the correlation coefficients (r) were less in patients with AML. In addition salivary S-IgA secretion rate was also inversely correlated with the age of healthy subjects. In contrast to salivary flow rate, the correlation between the age and the salivary S-IgA secretion rate was completely abolished in patients with AML before chemotherapy and after chemotherapy (correlation coefficients 0.007 and –0.031 respectively).

The salivary flow rate in patients with AML before chemotherapy was significantly lower by (26 %) than healthy subjects. Furthermore the salivary S-IgA secretion rate in patient with AML before chemotherapy was significantly lower by (8%) than their healthy counterparts as presented in table 3.

On chemotherapy, a further reduction in the salivary flow rate and salivary S-IgA secretion rate was detected. Salivary flow rate was significantly reduced after chemotherapy by (44%). In addition salivary S-IgA secretion rate was significantly reduced by (33%) after chemotherapy as presented in table 4.

It was clear that after chemotherapy, patients without mucositis have had a higher salivary S-IgA secretion rate by (9%) than their counterpart patients with various degrees of mucositis.

**DISCUSSION**

In the current study, the results obtained show a high incidence of ongoing changes in the oral
mucosa in AML patients. About half of studied patients showed signs of hemorrhagic phenomena on the oral mucosa, in most cases in the form of gingival bleeding, whereas only (5%) of patients demonstrated ecchymosis. In line with our results, out of 40 patients with acute leukemia examined by Djuric et al 61% of patients showed signs of hemorrhage on the oral mucosa, in most cases in the form of petechiae, whereas seven patients demonstrated spontaneous bleeding (17).

Oral infections in the current study were seen in 20% of AML patients before chemotherapy, and approximately in 32.5% of AML patients after chemotherapy. Despite no significant differences in oral infection incidence before and after chemotherapy, AML patients are more prone to infection after chemotherapy due to the direct action of the cytotoxic drug on oral tissues or its indirect effect on bone marrow and immunosuppression, or might be the result of a combination of the two effects. (18, 19).

In this study gingival enlargement was observed in 37.5% of AML patients before chemotherapy while it significantly went down to only 10% of the patients after chemotherapy. Al-Jubori found that 41% of leukemic patient complaining from gingivitis and gingival hypertrophy while Abdullah reported that gingival enlargements was observed in 31.4 % of acute leukemic patients (20, 21).

Similar to the findings reported in this study Demirer et al noticed that the gingival overgrowth due to acute leukemia normally improves by chemotherapy with peripheral blood values, without any periodontal treatment (22).

Black hairy tongue was found in 5% of AML patients before chemotherapy and in 10% of the patients after chemotherapy. This condition characterized by elongation of filliform papillae. It could be pseudo black caused by discoloration of the lingual coating resulting from medicaments, or due to the superficial pigmentation caused by decomposition of the blood from continuous oral bleeding (23, 24).

The current study showed a higher frequency of oral mucositis in AML patients (52.5%) during chemotherapy and the majority of patients showed grade 1 (25.5%), whereas grade 2, 3 and 4 appear less frequently (17.5%, 5% and 5% respectively). These results are similar to the findings reported by Chan et al who studied the oral complications in Chinese cancer patients undergoing chemotherapy and noticed that 22.3% of patients developed (grade 1) mucositis and 19.1% of them had grade 2 while only 1.1% and 2.1% of patients developed grade 3 and 4 respectively (25).

Labar et al reported that oral mucositis developed in 55% of leukemic patients (26) in addition, such frequency of mucositis has been observed in other similar researches (28, 27), while Raber-Durlacher et al found that the incidence of chemotherapy-induced mucositis has been reported to be between 30% and 75%, depending on the chemotherapeutic regimen (29).

**Salivary Flow Rate**

Complaints of a dry mouth (xerostomia) and diminished salivary output (salivary hypofunction) are common in elderly people as a result of a plethora of salivary gland disorders, medication and medical disorders. Interestingly, some data showed age-related changes in salivary constituents, while others showed age-stable production of salivary electrolytes and proteins in the absence of major medical problems and medication use (30, 31).

Furthermore, numerous studies discussed functional disturbance of salivary gland in relation to xerostomia in elderly people (32, 33). In agreement with these reported results, the present study showed that the salivary flow rate has negative correlation with the age in both control and patients groups. The finding showed a decrease in the correlation coefficient (r) in case of AML patients before and after chemotherapy. This indicates impairment in the relationship between the age and the salivary flow rate due to the impact of the disease itself and the combined effect of disease and cytotoxic drugs after chemotherapy.

This study also demonstrated decreased salivary flow rate in AML patients before chemotherapy by (26 %) than the flow rate in healthy subjects. This may possibly be due to the effect of anxiety and emotional stress in patients with AML. Such patients are known to be very anxious when the cytotoxic therapy starts (34). As well, emotional stress in examined patients can lead to the decrease of the salivary flow rate and this can be explained as having a sympathoadrenal effect on the salivary glands (35, 36).

Fever is another reason of reduction of the salivary flow rate as it is commonly present in many of AML patients at the time of diagnosis (37). The salivary flow rate and composition are dependent on a variety of factors, including state of nutrition and body water homeostasis. Thus, cancer patients suffering from insufficient nutrition and/or dehydration may experience impaired saliva secretion and changes in composition (38, 39, 40).

Few studies have examined the histological changes induced by chemotherapy on human and rodent salivary gland tissue in oral mucosa.
examined during autopsies on patients treated by chemotherapy for a variety of solid and hematological cancers, 50% of the patients had ductal dilatation, cyst formation within the glandular tissue, acinar degeneration and infiltration of inflammatory cells in minor salivary gland tissue. While in major salivary glands, interstitial fibrosis, vacuolization, swelling and nuclear degeneration of acinar and ductal cells were demonstrated (4).

Furthermore, it has been stated that the decreased flow rate may be due in part to the anticholinergic antiemetics prescribed mainly in the early phase of chemotherapy, after which the salivary glands and their flow rates showed an almost immediate return to normal (41).

On the other hand, Jensen et al found a significant reduction in unstimulated whole saliva flow rate in breast cancer patients during chemotherapy, and remained lower six months after chemotherapy as compared to baseline (15). In the current study, it was found also that the salivary flow rate significantly reduced after chemotherapy by 44% below the rate measured in patients before chemotherapy.

This study showed also that following chemotherapy, patients with AML complaining from various degrees of mucositis have a lesser salivary flow rate than patients without mucositis although this correlation is not significant. In line with our findings, salivary hypofunction has been linked to mucositis, which may be caused by insufficient antimicrobial factors and mucosal protectants. A study of 63 patients receiving chemotherapy conducted by McCarthy et al reported that low salivary flow rates at baseline and during cytotoxic therapy were associated with increased risk of mucositis (42).

However, there is some evidence to suggest that increased contact of saliva with mucosal surfaces may cause greater oral mucositis, which may be attributable to the role of saliva in transporting stomatotoxic drugs directly to the oral mucosal tissues.

Salivary S-IgA

The results of this study approved other previous studies, which concluded that there is a significant relationship between age and salivary S-IgA level in which the S-IgA level declined with age (43, 44).

This relationship between the age and the salivary S-IgA secretion rate was completely abolished in patients with AML before chemotherapy and after chemotherapy (correlation coefficient 0.006 and –0.031 respectively). This result indicates that the disease process itself in addition to chemotherapy have profound effects on the saliva impairing the relationship found between the age of the healthy subjects and their salivary S-IgA secretion rate.

According to the results of the current study, the salivary S-IgA secretion rate in patient with AML (before chemotherapy) was significantly lower by (8%) than their healthy counterparts. In agreement to above mentioned, Abrahamsson et al and Uram & Rosoff found that in patients with acute leukemia there are acquired IgA deficiencies, which is more likely due to the disease process itself (45, 46).

Janković et al investigated salivary immunoglobulins in cancer patients, and reported that salivary IgG/IgA ratio was altered due to the higher concentration of IgG, and a lower concentration of IgA in saliva comparing to the healthy individuals (47).

The results of this study indicate that following chemotherapy of patients with AML, a further reduction in the salivary S-IgA secretion rate was noticed and the salivary S-IgA secretion rate was significantly reduced by (33%) comparing to its value in patients before chemotherapy. Similar results of chemotherapy induced reduction of S-IgA salivary levels were also observed by other studies (13, 15, 48).

The salivary S-IgA originates from plasma cells located within the salivary gland tissue and a secretory component is produced in the acinar and ductal cells of the salivary glands and coupled to the IgA, subsequently the complex is secreted into saliva as secretory IgA (S-IgA) (49). Chemotherapy depressed the IgA producing plasma cells located within the salivary gland tissue or inhibited the immunoglobulin transport mechanism in the salivary gland cells (50).

According to Harrison et al and Karolewska et al the low concentration of S-IgA in patients undergoing antineoplastic treatment could be partly responsible for a higher risk of developing mucositis (48, 51). This finding was confirmed in this study, since AML patients without mucositis had a higher salivary S-IgA secretion rate upon chemotherapy by (9%) than their counterparts with various degrees of mucositis.
Table 1: Age and gender distribution of AML patients.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Group</th>
<th>Total</th>
<th>Mean years</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15 - 25</td>
<td>2</td>
<td>18</td>
<td>40.61</td>
</tr>
<tr>
<td></td>
<td>25 - 35</td>
<td>2</td>
<td></td>
<td>21.34</td>
</tr>
<tr>
<td></td>
<td>35 - 45</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 - 55</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 - 65</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65 - 75</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 - 85</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 - 25</td>
<td>7</td>
<td>22</td>
<td>33.14</td>
</tr>
<tr>
<td></td>
<td>25 - 35</td>
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<td></td>
<td>16.26</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 - 55</td>
<td>3</td>
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<td></td>
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<tr>
<td></td>
<td>55 - 65</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>65 - 75</td>
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</tr>
<tr>
<td></td>
<td>75 - 85</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
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<td>12</td>
<td>18</td>
<td>36.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td>18.84</td>
</tr>
</tbody>
</table>

Table 2: Clinical oral findings in patients with AML before and after chemotherapy.

<table>
<thead>
<tr>
<th>Clinical Oral Findings</th>
<th>Before CTX No. (%)</th>
<th>After CTX No. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Hemorrhage</td>
<td>17 (42.5)</td>
<td>21 (52.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Petechiae</td>
<td>7 (17.5)</td>
<td>3 (7.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>12 (30)</td>
<td>20 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral Infections</td>
<td>8 (20)</td>
<td>13 (32.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Candidal thrush</td>
<td>5 (12.5)</td>
<td>9 (22.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>1 (2.5)</td>
<td>2 (5)</td>
<td>NS</td>
</tr>
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<td>Herpes labialis</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Black Hairy Tongue</td>
<td>2 (5)</td>
<td>5 (12.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Gingival Enlargement</td>
<td>15 (37.5)</td>
<td>4 (10)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pale Mucosa</td>
<td>13 (32.5)</td>
<td>9 (22.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>21 (52.5)</td>
<td>0.000001</td>
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</table>

Table 3: Statistical analysis (unpaired t-test) of the study parameters between control group and AML patients group before chemotherapy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No.</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow Rate (ml/min)</td>
<td>20</td>
<td>0.1</td>
<td>0.3</td>
<td>0.221</td>
<td>0.059</td>
<td></td>
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<tr>
<td>SIGA Secr. Rate (µg/min)</td>
<td>20</td>
<td>34.8</td>
<td>51.9</td>
<td>42.317</td>
<td>5.187</td>
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<tr>
<td>Flow Rate (ml/min)</td>
<td>40</td>
<td>0.08</td>
<td>0.3</td>
<td>0.165</td>
<td>0.054</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>SIGA Secr. Rate (µg/min)</td>
<td>40</td>
<td>32</td>
<td>46.9</td>
<td>38.968</td>
<td>3.858</td>
<td>P&lt;0.007</td>
</tr>
</tbody>
</table>

Table 4: Statistical analysis (paired t-test) of the study parameters between AML patients group before and after chemotherapy.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No.</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
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<td>SIGA Secr. Rate (µg/min)</td>
<td>40</td>
<td>32</td>
<td>46.9</td>
<td>38.968</td>
<td>3.858</td>
<td></td>
</tr>
<tr>
<td>Flow Rate (ml/min)</td>
<td>40</td>
<td>0.05</td>
<td>0.15</td>
<td>0.092</td>
<td>0.027</td>
<td>P&lt;1.5E-14</td>
</tr>
<tr>
<td>SIGA Secr. Rate (µg/min)</td>
<td>40</td>
<td>20.8</td>
<td>31.7</td>
<td>25.949</td>
<td>3.136</td>
<td>P&lt;2.5E-26</td>
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Figure 1: The percentage of various grades of mucositis developed in AML patients after chemotherapy

REFERENCES