Research Paper

Volume : 4 | Issue : 10 | October 2015 • ISSN No 2277 - 8179

Risk Factors of Oral Mucositis in Pediatric Patients (Less Than 18 Years Old) Receiving Chemotherapy

Medical Science

KEYWORDS : oral mucositis, risk factor, chemotherapy, pediateric and adolescent

Dr.Khadija M Ahmed	Lecturer University of Sulaimani, Faculty of Medical Sciences, School of Dentistry, Oral Diagnosis Department.
Dr. Basil K Abdulla	Hiwa Hospital, Clinical Pediatric Hematologist and Oncologist, Sulaimani City, Iraq.
Dr. Tara K Saber	Dentist, Directorate of Health, Sulaimani City, Iraq.
Dr. Miwan Salahalddin A. Alrahman	Lecturer University of Sulaimani, Faculty of Medical Sciences, School of Dentistry, Conservative Department.

ABSTRACT

Background: *Mucosal barrier injury (mucositis) is a common complication of many treatments used in hematologic and solid malignancies, affecting most patients whose neoplasms are treated with intensive chemotherapy. Mucositis has been identified as a critical risk factor for infections and is a major driver of analgesic and total parenteral nutrition use. Several risk factors affect the development and severity of oral mucositis in cancer patients receiving chemotherapy.*

Objectives: The objectives of the present study were to determine the incidence and risk indicators for oral mucositis in pediatrics and adolescent patients receiving chemotherapy.

Methods: *Across-sectional survey was carried out on pediatrics patients receiving different chemotherapy regimens at Hiwa hospital in Sulaimani city between April and August 2014. The degree of mucositis was recorded by WHO Common Toxicity Criteria (CTC). Potential risk indicators for the development of oral mucositis were include age, gender, tumor types, treatment types, neutrophile count, liver enzymes, serum creatinin and bilirubin levels. The status of oral hygiene was evaluated using oral hygiene index and gingival index. The associations between mucositis and risk indicator variables were tested using a (chi-square) test and Odd ratio.*

Results: *Of the 104 patients enrolled; 73patients showed mucositis grade<2 and 31 patients had grade ≥ 2. Male gender was predominant in both groups of mucositis. The majority of the patients had been diagnosed with solid tumor (52.9 %) and almost received Etoposide-based regimen. Patients with neutropenia, altered renal function tests, those with poor oral hygiene and epithial damage were highly significantly associated with incidence of oral mucositis grades≥ 2.*

Conclusions: *Our findings suggest that children who are neutropenic, those with serum creatinin and bilirubin elevation, and those with poor oral hygiene are at greater risk of developing oral mucositis.*

Introduction:

Because of its capacity to affect cells with high replication rates, chemotherapy has remained the mainstay of treatment for patients with advanced malignant disease incurable by local surgery or radiotherapy. Effective use of chemotherapy is limited by its toxic effects including nausea, vomiting, diarrhea, oral mucositis,and myelosuppression(Sharma et al., 2005; Djavidet al., 2011).

Oral mucositis (OM) is considered as a painful and often debilitating side effect of chemotherapy and radiation therapy occurring in patients with cancer. It is also a frequent problem for those receiving myeloablative conditioning regimens prior to hematopoietic stem cell transplantation (Sonis, 2004a).

Clinically, the most common signs and symptoms of OM are erythema, edema, burning sensation, increased sensitivity to hot and spicy foods, white patches on mucous membranes of the cheeks, lips, tongue and palate, and subsequent painful ulcers. The latter makes it hard to swallow, which leads to malnutrition and dehydration, consequently affecting mucosal regeneration (Sonis, 2004a). Furthermore, patients treated with myelosuppressive chemotherapy are already at increased risk of infection due to neutropenia, and breakdown of the mucosal barrier due to OM which exacerbates the incidence of bacteraemia and sepsis (Eltinget *al.*, 2003; Sonis, 2004b).

Oral mucositis has great impact on a patient´s well-being. It may necessitate modifications of treatment planning, suspension of chemotherapy, need for opioid analgesics, and/or require enteral or parenteral nutrition. Accordingly, all these will impose extra impact on the quality of life of cancer patients (Stone *et al.,* 2007; Bjordalet *al.,* 2010).

It is generally accepted that oral mucositis is multifactorial in nature. Cancer treatment factors such as type and dosage of chemotherapy and patient-related factors such as, age, gender, neutrophil count, and level of oral care, are all thought to have a major impact on oral mucositis (Wardleyet *al.,* 2000; Barasch and Peterson, 2003; Sonis*et al.*, 2004). Chemotherapeutic drugs that are cell-cycle specific interfering with either DNA, RNA, or protein synthesis are associated with an increased risk of oral mucositis. Methotrexate, Etoposide and Melphalan, which are secreted in the saliva, are associated with high rate of severe oral mucositis (Cheng *et al.*, 2008).

Pediatric and adolescent patients make up an important group of cancer populations with increased annual incidence rates (Linabery and Ross, 2008). While cytotoxic agents including Adraimycin, Etoposide, and Methotrexate are the mainstay choices of chemotherapy to treat various childhood cancers, they are also associated with oral mucositis. In addition, pediatric and adolescent patients typically have a higher proliferating fraction of basal cells than adults, and they may therefore be at increased risk of OM (Niscola*et al.,* 2007; Cheng *etal.*, 2013).

Though precise incidence data pertinent to this population are limited, this study was conducted to identify risk indicators and side effects of oral mucositis in a pediatric population receiving chemotherapy in our locality.

Aims of the study:

The present study aimed to determine the incidence and risk factors associated with OM in pediatric and adolescent patients receiving chemotherapy for cancer.

Patients and methods

1. Study patients:

This study was conducted in Hiwa Hospital in Sulaimani City, after approval from the ethics committee (School of Dentistry,

University of Sulaimani). Between April 2014 and August 2014, a total of 104 inpatients with solid and hematological tumors receiving chemotherapy were recruited.

The study was conducted in accordance with the Declaration of Helsinki; all the children and adolescents gave their assent to participate and their parents provided written informed consent before enrolment in the study.

Eligible patients were children and adolescents under the ages of 18 years who had started chemotherapy. The following criteria were used to select the patients:

2. Inclusion criteria:
- Children and adults who were hospitalized to start chemotherapy (Inpatients).
- Those who were treated with aggressive stomatoxic chemotherapy (i.e. Etoposide, Methotrexate, Adraimycin, Cytosar) during the induction or consolidation phase.
- Those who agreed to participate in the study.

3. Exclusion criteria:
- Children and adolescents who were not hospitalized (out patients).
- Those who were treated with lower dose stomatoxic chemotherapy.
- Those who refused to participate in the study.

4.Baseline Examination:
Baseline data (age, gender, original cancer site, chemotherapy regimen, mean absolute neutrophil count ANC, white blood cell WBC count, Aspartate amino transferase ASAT, alanin amino transferase ALATand creatinin value) were all collected during the first five days of receiving chemotherapy.

Leukopenia was defined as a white blood cell count $\leq 3.9 \times 10^9/L$ and classified according to the WHO criteria. The exact values of absolute neutrophil count (ANC), ASAT/ALAT and creatinin were converted to a toxicity grade according to the WHO guidelines and further categorized into grade 0, 1-2 or 3-4.

5. Oral mucositis measurement:
The study has utilized the World Health Organization (WHO) mucositis scoring system to assess oral mucositis. The WHO scale is an overall rating of oral mucositis using five grades (grades 0-4). Grade 0= no change; grade 1= localized erythema of oral mucosa; grade 2= diffuse erythema, discrete erosive lesions, can eat solids; grade 3= Diffuse erythema, diffuse erosive lesions, ulceration, requires liquid diet only; grade 4= Multiple ulcers, necrosis of oral mucosa, alimentation not possible.

All patients were examined for the development of oral mucositis two times per week. Results were recorded on medical records.

6. Oral Health condition:
The oral health condition of each patient was assessed using oral hygiene index OHI and gingival index GI.

The OHI was performed by placing a dental explorer onto the distal part of the tooth surface and drawing it to the medial part on the facial as well as on the oral side of each present tooth. Both facial and oral sides of the tooth were separately considered a scoring unit. The criteria for scoring were as follows (OHI):

0=No plaque and calculus on the tooth surfaces
1=Plaque and calculus on the gingival third of tooth surface
2=Plaque and calculus on the middle third of tooth surface
3=Plaque and calculus on the incisal third of tooth surface

The OHI score per person was obtained by totaling the scores per tooth surfaces and dividing it by the number of surfaces examined.

The GI was performed by observing the signs and symptoms of inflammation on the gingival tissue surrounding each tooth. Marginal gingiva, attached gingiva, and medial papilla on the facial, as well as on the oral side of each present tooth, was considered a scoring unit. The criteria for scoring were as follows (GI):

0= Absence of signs of inflammation
1= Mild to moderate inflammation, slight change in color, slight edema
2= Mild to moderately severe inflammation, redness, edema, and glazing
3= Severe inflammation, marked redness and edema with tendency to bleeding, and ulceration.

The GI score per person was obtained by totaling the scores per gingival units and dividing it by the number of units examined.

Further evaluations of the oral condition were performed using artificial white light (torch) to detect any area of epithelial damage.

Patients were also asked about tooth brushing and use of interdental cleansing devices or antifungal agents, in order to determine individual patients' care of their oral health.

7. Statistical analysis:
The collected data were entered into a Microsoft Excel Spreadsheet, and after cleaning were transported into the SPSS (Statistical Package for the Social Sciences-version21.0) software program for statistical analysis.

Descriptive statistics (numbers and percentage) were calculated for all variables, and statistical analysis was also applied to find associations between variables using Chi-square test. A p-value < 0.05 was considered as significant.

Risk estimation was calculated by using the Odds ratio through cross tabulation, with 95% confidence intervals.

1. Patient characterization:
There were 104 patients in the analytical sample (72 males and 32 females).

Table 1 describes the characteristics of the patients included in this study and their types of treatments. More of the patients were less than 8 years old (58.7%) compared to over 8 years old (41.3%) and the majority of the participants were boys [72(69.2%)].

More than half of the patients had been diagnosed with hematological malignancies [54(51.9%)] and the majority of the subjects had been treated with Etoposide-based chemotherapy [55(52.9%)], followed by Methotrexate (MTX) [24(23.1%)], Anthracycline [6(5.8%)] and Cytosar based regimen [4(14.4%)].

More of the patients had no previous experience of oral mucositis [62 (59.6%)] compared to those who had experienced oral mucositis in other cycles of chemotherapy, as shown in table 1.

Volume : 4 | Issue : 10 | October 2015 • ISSN No 2277 - 8179

Table 1: Patient characteristics, types of tumor, types of chemotherapy and blood groups

Variables	Frequencies(No.)	Percentages (%)
Age groups		
0-8	61	58.7
More than 8	43	41.3
Total	104	100.0
Sex		
Male	72	69.2
Female	32	30.8
Total	104	100.0
Types of tumor		
Hematological tumor	54	51.9
Solid tumor	50	48.1
Total	104	100.0
Types of chemotherapy		
Etoposide	55	52.9
MTX	24	23.1
Anthracycline	6	5.8
HDC	15	14.4
Combined	4	3.8
Total	104	100.0
Blood groups		
A	31	29.8
B	18	17.3
AB	13	12.5
O	42	40.4
Total	104	100.0
Rh group		
+ve	98	94.2
-ve	6	5.8
Total	104	100.0
Past history of OM		
Yes	42	40.4
No	62	59.6
Total	104	100.0

MTX: Methotrexate.
HDC:high dose cytosar, MTX: Methotrexate.

2. Association between OM grade and various types of chemotherapy:
As shown in table 2, the majority of patients were treated with Etoposide-based regimen (55patients); 38 patients developed OM grade <2and17 patients developed OM grade ≥2. Among those pediatric patients receiving MTX based regimen, the second most common chemotherapeutic drug treatment (24 patients), 15 had a WHO score <2 and 9 patients, with OM grades≥2.

Table 2: Association between OM grade and various types of chemotherapy

Types of chemotherapy <2 ≥2			WHO scores		Total
Types of chemotherapy	Etoposide	Count	38	17	55
		% within WHO scores	52.1%	54.8%	52.9%
	MTX	Count	15	9	24
		% within WHO scores	20.5%	29.0%	23.1%
	Anthracycline	Count	3	3	6
		% within WHO scores	4.1%	9.7%	5.8%
	HDC	Count	13	2	15
		% within WHO scores	17.8%	6.5%	14.4%
	Combined	Count	4	0	4
		% within WHO scores	5.5%	0.0%	3.8%
Total		Count	73	31	104
% within WHO scores			100.0%	100.0%	100.0%

MTX: Methotrexate.
HDC: High Dose cytosar.

3. Association between OM grade and various risk factors (part 1)
The Odds ratio (OR), with 95% confidence interval (CI), was estimated for some associated risk factors as shown in table 3.Of the 104 pediatric patients in the sample, 31 recorded an oral mucositis WHO score ≥2; of these 24(33.3%) were males and 7(21.9%) were females (OR= 0.5; 95% CI = 0.21-1.47) that is to say there were no significant differences between males and females in terms of developing oral mucositis.

Pediatric and adolescent patients above 8 years of age were more prone to develop severe grades of oral mucositis than children below 8 years of ages (OR=2.1; 95% CI = 0.93-5.1) but the results were statistically insignificant (P= 0.06). Regarding the types of tumor, results showed that patients who received chemotherapy for solid tumors had a slightly increased risk of developing OM compared to those with hematological tumors (OR=1.22; 95% CI=0.52-2.83).

Patients with –ve Rh blood groups, those who had poor oral hygiene and those who had neglected their oral health were more likely to record a WHO score ≥2 OM [(OR= 2.5;95% CI=0.47-13.1); (OR=4.32; 95% CI=1.7-10.6); (OR=1.7; 95% CI=0.65-4.5) respectively].

In contrast, past history of oral mucositis and presence of areas of epithelial damage were not associated with an increased risk of developing severe grades of oral mucositis [OR= 0.62; 95% CI=0.26-1.4); (OR=0.16; 95% CI=0.06-0.41) respectively].

Table 3: Association between OM grade and various risk factors (part1):

Variables	WHO scores <2 N (%)	WHO scores ≥2 N (%)	OR(95%CI)	P values
Sex Male Female	48(66.7%) 25(78.1%)	24(33.3%) 7(21.9%)	0.5 (0.21-1.47)	0.238
Age groups 0-8 More than 8	47(77.0%) 26(60.5%)	14(23.0%) 17(39.5%)	2.1(0.93-5.1)	0.069
Types of tumor Hematological tumor Solid tumor	39(72.2%) 34(68.0%)	15(27.8%) 16(32.0%)	1.22(0.52-2.83)	0.638
Rh group +ve -ve	70(71.4%) 3(50.0%)	28(28.6%) 3(50.0%)	2.5(0.47-13.1)	0.265
Past history of OM Yes No	27(64.3%) 46(74.2%)	15(35.7%) 16(25.8%)	0.62(0.26-1.4)	0.278
Status of oral hygiene Good Poor	57(80.3%) 16(48.5%)	14(19.7%) 17(51.5%)	4.32(1.7-10.6)	0.001
Epithelial-damage Yes No	11(40.7%) 62(80.5%)	16(59.3%) 15(19.5%)	0.16(0.06-0.41)	<0.001
Oral health care Yes No	59(72.8%) 14(60.9%)	22(27.2%) 9(39.1%)	1.7(0.65-4.5)	0.268

Data are presented as number (percentage).
OR odds ratio, CI confidence interval.
P≤0.05 significance.

4. Association between OM grades and various risk factors (part 2)

The Odds ratios (OR),with 95% confidence interval (CI), of the other associated risk factors are shown in table 4.Generally high OM (grades ≥2) and odds ratios were reported among those patients with grade ≥ 2of neutropenia and alteration in renal and liver function results (grade≥ 2). Moreover, pediatric and adolescent patients with gingival and plague scores ≥2 were at high risk of developing severe grades of oral mucositis (OR=3.6; 95% CI=1.4-9.4) and the results were statistically highly significant (p=0.005).

Table 4: Association between OM grade and various risk factors (part2)

Variables	WHO scores		OR(95%CI)	P values
	<2 N (%)	≥2 N (%)		
Grades of neutropenia <2 ≥2	53(73.6%) 20(62.5%)	19(26.4%) 12(37.5%)	1.6 (0.68 - 4.03)	0.253
Renal function grades <2 ≥2	58(73.4%) 15(60.0%)	21(26.6%) 10(40.0%)	1.8(0.77-4.7)	0.201
Liver function <2 ≥2	71(70.3%) 2(66.7%)	30(29.7%) 1(33.3%)	1.1 (0.10 - 13.5)	0.892
Gingivalscore <2 ≥2	61(77.2%) 12(48.0%)	18(22.8%) 13(52.0%)	3.6(1.4-9.4)	0.005
Plaque score <2 ≥2	61(77.2%) 12(48.0%)	18(22.8%) 13(52.0%)	3.6(1.4-9.4)	0.005

Data are presented as number (percentage).
OR odds ratio, CI confidence interval.
P≤0.05 significance

Discussion:

Oral mucositis and associated risk factors:

To the best of our knowledge, this is the first study in our country to evaluate the risk factors of oral mucositis in pediatric cancer populations. Whilst two previous studies in this field have been conducted, their study populations predominantly consisted of adult patients. Mucositis in pediatric and adolescent cancer patients is relatively understudied and few studies are even available in the literature worldwide (Cheng *et al.*, 2011).

According to the Pathophysiology of oral mucositis suggested by Sonis *et al.* (2004), mucositis is a complex biological procedure. The risk of oral mucositis varies greatly; therefore, being able to predict patients at risk of developing OM would help identify subsets of patients who might benefit from preventive strategies for OM in the future and it may also help select and stratify patients in future OM efficacy trials.

Cancer therapy-related OM is a frequent morbid condition of patients undergoing chemotherapy. The results of this study demonstrated that among all patients incidence of OM was 29.8%. Whilst this finding is consistent with results reported by (Faddae*t al.* 2006; Raber-Durlacher*et al.* 2000; Figliolia*et al.*, 2008), higher percentages of OM were recorded by Cheng *et al.* (2011). This result could be attributed to the fact that we did not interfere with the hospital's program to prevent occurrence of severe OM, and for ethical purposes all patients received prophylactic treatment for OM in the form of Italian solution [(a mixture of vit. B complex, Folic acid, Normal saline, Mycostatin drop, Hydrocortisone, NaHCO3 (Sodium bicarbonate), Lidocaineampol)].

Although it is well established that patients with hematological malignancies are at risk of developing oral mucositis, the results of this study showed that there was no difference between patients with hematological and solid tumors and it seems that both groups of patients are at risk of developing oral lesions. Comparable results to our findings are reported by Cheng *et al.* (2001 and 2011).

This study showed a higher frequency of ulcerated OM (39.5%) in children aged more than 8 years compared with patients aged less than 8years, despite these differences not being significant. These results are comparable with findings of Cheng *et al* .(2011) and in contrast with other studies (Scully *et al.*, 2006; Figliolia*et al.*, 2008) that have observed that this stomatologic complication most frequently affects children below 8 years of age. This might be due to the fact that mucositisis multifactorial in nature and all age groups might be susceptible.

In the present study higher frequency of chemotherapy–induced OM (33.3%) was noted in males than females, although the difference was insignificant statistically. Our data are not concordant with those of Vokurka*et al.*(2006), who suggested that females appear to be more susceptible to this post-chemotherapy complication and that gender may play an important role as an independent risk factor and as a predictor for oral mucositis in high-dose chemotherapy settings. In addition our findings are consistent with (Figliola*etal.*, 2008; Cheng *et al.*, 2011; Barasch and Peterson, 2003; Fadda*et al.*, 2006) who concluded that it remains unclear as to how the combined risk factors of age and gender affect the incidence and severity of oral mucositis in chemotherapy treated patients.

It should also be borne in mind that the incidence of mucositis is likely to be influenced by the type of chemotherapy; this investigation showed that treatment of pediatric patients with Etoposide or Methotrexate based regimen was associated with increased frequency of ulcerated mucositis compared to the other treatment regimens. This could be explained by the fact that since these two drugs have a direct stomatotoxic effect and are secreted in the saliva, they are therefore associated with high rate of severe oral mucositis.

In contrast to the study reported by Cheng *et al.* (2011), prior history of oral mucositis and presence of epithelial damage were not associated with severe OM. This result is plausible considering the genetic diversity in susceptibility to OM and due to underestimation of OM in our country.

The findings of the present study also suggest that neutropenia and altered liver and renal function during stomatotoxic chemotherapy play a role in the etiology of OM in children and adolescents. These factors may play a synergistic role in the etiology of OM, reflecting the multifactorial nature of oral mucositis.

Odds ratio values suggest that neutropenia may be the most important of these three risk factors. This finding is consistent with findings by Cheng *et al.* (2008; 2011). However, Ramirez-Amador and colleagues (2010) found no association between OM severity and neutrophile count.

The importance of normal neutrophile count is consistent with our current understanding of indirect cytotoxicity and the biological process involved in the pathogenesis of OM as demonstrated by Sonis *et al.* (2004). It has been suggested that a decrease in the neutrophil count may result in an impaired ability to protect against oral mucosal damage, and may affect the proliferation of oral epithelial cells. In addition, neutropenic patients are at increased risk of microbial colonization of damaged mucosal surfaces, resulting in increased proinflammatory cytokines in oral mucosa, which may aggravate OM. Moreover,

studies incorporating the use of systemic hematopoietic growth factors in regimens to accelerate neutrophil recovery and its function in frequently reducing OM have supported this hypothesis. Nevertheless, it is possible that to some extent the association between neutropenia and OM is related to the dose-intensity of the chemotherapy regimen used and requires further study.

Although our results showed that alteration in liver function was less associated with occurrence of mucositis, it is nevertheless believed that OM occurs when liver toxicity is substantially high in children. Our finding differs from results reported by Cheng *et al.* (2008). One possible explanation for this finding is that fewer children were treated with MTX and anthracycline antibiotics like doxorubicin. These treatment modalities are largely metabolized by the liver and in the presence of liver dysfunction these drugs accumulate within the cell body.

Oral hygiene condition and oral mucositis:
The present study showed that pediatric and adolescent patients with poor oral hygiene and those with high OHI and GI scores were at increased risk of developing more severe OM and the results were statistically highly significant.

This result was not surprising since no patients in this study cohort had undergone dental evaluation and treatment prior to the start of cancer chemotherapy. Until now, dentists have played no role in managing cancer patients at Hiwa Hospital.

There has been much emphasis in the literature on association between application of systematic and preventive oral care for cancer patients during chemotherapy and reduction in the incidence and severity of oral mucositis (Cheng *et al.*, 2001; Djuric*et al.*, 2006; McGuire *et al.*, 2006; Santos *et al.*, 2011).

Moreover, mucositis guidelines from the Multinational Association for Supportive Care in Cancer/ International Society of Oral Oncology recommended systematic oral care with brushing, flossing, bland rinses and moisturizers, as reported by Keefe *et al.*, (2007).

These guidelines also recommend a multidisciplinary approach to oral care including physicians, dentists, dental hygienists, nurses, pharmacists and other relevant professionals. Hereby we call for initiation of appropriate dental programs for all patients before and during administration of chemotherapy.

REFERENCE

*Barasch A and Peterson DE (2003). Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. Oral Oncol; 39:91-100 (and references cited therein). *BjordalJM, BensadounRJ, TunèrJ,FrigoL,GjerdeK, Lopes-Martins RA (2011). A systematic review with meta-analysis of the effectof low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis.Support Care Cancer; 19:1069–1077. * Cheng KKF,Molassiotis A, Chang AM,WaiWC, Cheung SS (2001). Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients.Eur J Cancer 37:2056–2063. *Cheng KKF, Lee V, Li CH, Goggins W, Thompson DR, Yuen HL et al.,(2011). Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. Oral Oncol 47:153–162*Cheng KKF, Lee V , Li CH, Yuen HL, Ip WY, He HG, Epstein JB (2013). Impact of oral mucositis on short-term clinical outcomes in paediatric and adolescent patients undergoing chemotherapy.SupportCareCancer21:2145–2152. *Cheng KKF, Goggins W B, Lee V and Thompson D R (2008). Risk factors for oral mucositis in children undergoing chemotherapy: A matched case-control study. Oral Oncology; 44, 1019– 1025 *Djavid GE, Emami A, Fashtami LA, Safaeinodehi S, Baiat FM, Fateh M, Zand N (2011).Low Level Laser Therapy in Management of Chemotherapy- Induced Oral Mucositis: Prophylaxis or Treatment.Journal of Lasers in Medical Sciences;2:12-17. *Djuric M, Hillier-Kolarov V, Belic A, Jan-kovic L(2006). Mucositis prevention by improveddental care in acute leukaemia patients. Support CareCancer; 14:137–40. *Elting L, Cooksley C, Chambers M, Cantor S, Manzullo E and Rubenstein E (2003). The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis.Cancer; 98:1531–1539. *Fadda G, Campus G and Lug lie P (2006). Risk factors for oral mucositis in paediatric oncology patients receiving alkylant chemotherapy. BMC Oral Health; 6:13. *Figliolia SLC, Oliveira DT, Pereira MC (2008). Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients. Oral Dis 14:761–766 * Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA et al (2007).Updatedclinicalpracticeguidelines for the prevention andtreatment of mucositis. Cancer 109:820–831 *Linabery AM, Ross JA (2008).Trends in childhood cancer incidence in the U.S. Cancer 112:416–43 * McGuire DB, Correa ME, Johnson J, Wienandts P.(2006). The role of basic oral care and good clinical practice principles in the management of oral mucositis. Support Care Cancer; 14:541–547. *Niscola P, Romani C, Cupelli L, Scaramucci L, Tendas A,DentamaroT, et al. (2007).Mucositis in patients with hematologic malignancies: an overview. Haematological/the haematology journal; 92(02):222-231 *Raber-Durlacher JE, Weijl NI, Abu Saris M, de Koning B, Zwinderman AH and Osanto S (2000). Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Supp Care Cancer; 8: 366–71. *Ramírez-Amador V, Anaya-Saavedra G, Crespo-Solís E,et al.,(2010). Prospectiveevaluation of oral mucositis in acute leukaemia patients receiving Chemotherapy. Support Care Cancer; 18:639–46. *Santos P,Coracin F, Barros J, Dulley F, Nunes F, Magalha˜es M (2011). Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis.Clin Transplant: 25: 325–328. *Scully C, Sonis S and Diz PD (2006). Oral mucositis.Oral Dis; 12:229–241*Sharma R, Tobin P, Clarke SJ (2005). Management of chemotherapy-inducednausea, vomiting, oral mucositis, and diarrhoea.Lancet Oncol, 6:93-102 *Sonis ST (2004a). Oral mucositis in cancer therapy. J Support Oncol; 2(suppl3):003–008 *Sonis ST (2004b): Pathobiology of mucositis. SeminOncol Nursing; 20: 11–15. *Sonis ST, Elting LS, Keefe D, et al.(2004). Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer;100(suppl):1995–2025. *StoneR,Potting M,Clare S,Uhlenhopp M, Davies M,Mank A,Quinn B(2007).Management of oral mucositis at European transplantation centres. Can OncolNurs J; 11, 53-59. Vokurka S, Bystricka E, Koza V,et al.(2006). Higher incidenceof chemotherapy induced oral mucositis in females: asupplement of multivariate analysis to a randomized multicentre study. Support Care Cancer14:974–976. *Wardley AM, Jayson GC, Swindell R, Morgenstern GR, Chang J, Bloor R, et al. (2000). Prospective evaluation of oral mucositis in patients receiving Myeloablative conditioning regimens and haemopoietic progenitor rescue.Br J Haematology; 110(2):92-99.