Oral mucositis in paediatric patients after chemotherapy for cancer

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KEY MESSAGES

1. Oral mucositis (OM) is common among paediatric patients receiving chemotherapy.
2. Paediatric patients who are neutropaenic, with high levels of anxiety, or with a history of OM have a greater risk and an earlier onset of OM.
3. OM has negative effects on clinical outcomes and the patient's life, including on oral function and quality of life.

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Introduction

Oral mucositis (OM) can aggravate the paediatric patients' clinical condition and elicit multiple debilitating oral symptoms that irrevocably alter patients' quality of life.[1,2] Nonetheless, the full spectrum of pathogenesis and factors in the development of OM remains poorly understood, in particular in the paediatric cancer population. This study aimed to determine the factors associated with OM in paediatric patients undergoing chemotherapy for cancer, and to compare the outcomes in paediatric patients with and without OM.

Methods

This was a multi-centre, prospective, observational cohort study conducted from November 2007 to November 2009 in a university-affiliated hospital and two regional hospitals in Hong Kong. This study was approved by the Institutional Review Boards of the hospitals, and was conducted in accordance with the Declaration of Helsinki. Written informed parental consent was obtained for each subject before enrolment. A total of 88 boys and 52 girls aged 6 to 18 (mean, 11.8; standard deviation [SD], 3.3) years who underwent stomatotoxic chemotherapy for cancer were recruited through convenience sampling. Most (56%, n=78) were diagnosed with haematological malignancies, and most (28%, n=39) were treated with adriamycin-based chemotherapy.

Subjects were asked to use a daily diary to complete the Chinese version of the mouth and throat soreness (MTS)-related questions of the Oral Mucositis Daily Questionnaire from the start of chemotherapy (day 1) to day 14, the Chinese version of the State Anxiety Scale for Children on day 1, and the Oropharyngeal Mucositis Quality of Life Scale (OMQoL) at baseline, day 7, and day 14. Demographic and clinical data were collected from interviews and subjects' medical records. Binary and ordinal logistic regression analyses were used to assess the relation between potential factors and risk of OM occurrence. The Cox proportional hazards regression model was used to determine the effect of potential factors on time in days to onset of OM. Differences in proportions of subjects manifesting adverse clinical and patient-reported outcomes between subjects with, and without OM and by severity of OM were compared using the Chi-square test, one-way ANOVA, and multi-level modelling techniques.

Results

Incidence, onset, and severity of oral mucositis

Overall, 41% (n=57) of paediatric patients developed OM (Table 1). Of these, 23% (n=32) reported a maximum MTS score of 2 (non-severe OM), and 18% (n=25) reported a maximum MTS score of 3-4 (severe OM). The mean time to onset of OM was 4.7 (SD, 2.7; range, 2-9; 95% confidence interval [CI], 4.0-5.4) days after the start of chemotherapy, with a mean duration of 6.3 (SD, 4; range, 1-13; 95% CI, 5.2-7.4) days and with the peak at day 7.5 (SD, 2.6; range, 4-11; 95% CI, 6.8-8.2). The mean area under the curve (AUC) MTS score across 14 days was 16.9 (SD, 6.5; range, 2.5-28.5; 95% CI, 15.1-18.6).

TABLE 1. Characteristics of paediatric patients with or without oral mucositis (OM) after chemotherapy

Variable	No. (%) of patients		
	Absence of OM (mouth and throat soreness [MTS] score of<2) [n=83]	Presence of OM (MTS score of ≥2) [n=57]	Total (n=140)
Age (years)			
6-12	43 (51.8)	32 (56.1)	75 (53.6)
13-18	40 (48.2)	25 (43.9)	65 (46.4)
Gender			
Boys	53 (63.9)	35 (61.4)	88 (62.9)
Girls	30 (36.1)	22 (38.6)	52 (37.1)
Education level (n=135)			
Primary 1-3	17 (21.2)	6 (10.9)	23 (17)
Primary 4-6	34 (42.5)	19 (34.5)	53 (39.3)
Secondary 1-3	19 (23.8)	21 (38.2)	40 (29.6)
Secondary 4-7	10 (12.5)	9 (16.4)	19 (14.1)
Cancer diagnosis			
Solid tumours	42 (50.6)	20 (35.1)	62 (44.3)
Haematological malignancies	41 (49.4)	37 (64.9)	78 (55.7)
Cancer regimen			
Etoposide-based regimen	15 (18.1)	3 (5.3)	18 (12.9)
Methotrexate-based regimen	11 (13.3)	14 (24.6)	25 (17.9)
Cytarabine-based regimen	9 (10.8)	4 (7.0)	13 (9.3)
Adriamycin-based regimen	22 (26.5)	17 (29.8)	39 (27.9)
Other anthracycline-based regimen	7 (8.4)	6 (10.5)	13 (9.3)
Combined etoposide, methotrexate, cytarabine and/or adriamycin regimen	19 (22.9)	13 (22.8)	32 (22.9)

Factors associated with oral mucositis

Paediatric patients with and without OM were similar with regard to age, gender, oral care, traditional Chinese medicine consumption, renal functional status, use of growth factor, and extent of nausea and vomiting (P>0.25, Table 2). Paediatric patients with OM were more likely to have haematological malignancies and a low consumption of sweet food than those without OM (P<0.25). The univariate analysis revealed that a history of OM, a higher level of anxiety, ≥1 neutropaenia, and ≥1 liver toxicity significantly increased the risk of developing OM (P<0.05).

A history of OM, sweet food consumption, anxiety, cancer diagnosis, absolute neutrophil count, and aspartate aminotransferase to alanine aminotransferase ratio all had values of P<0.25 in the univariate models and were included as candidate variables for the multivariate model, adjusting for potential confounding factors of the chemotherapy regimen. In the multivariate model, only a history of OM (adjusted odds ratio [OR], 3.94; 95% CI, 1.49-10.39), a higher level of anxiety (adjusted OR, 1.46; 95% CI, 1.23-1.73), and grade 1-2 (adjusted relative risk [RR], 4.59; 95% CI, 1.81-11.66) and 3-4 (adjusted RR, 9.19; 95% CI, 1.83-46.29) neutropaenia were significantly associated with a higher probability of OM, after controlling for the chemotherapy regimen (P<0.01).

The AUC MTS score was categorised into three ordinal subgroups of 0 (n=55), 1-11.5 (n=39), and ≥12 (n=46). The results of these subgroups were consistent with the binary logistic regression model. A history of OM (adjusted OR, 2.43; 95% CI, 1.14-5.18, P=0.02), a higher level of anxiety (adjusted OR, 1.37; 95% CI, 1.20-1.55, P<0.001), and grade 1-2 (adjusted OR, 2.93; 95% CI, 1.41-6.10, P=0.004) and 3-4 (adjusted OR, 8.69; 95% CI, 2.12-35.69, P=0.003) neutropaenia were significantly associated with a higher category of AUC MTS, after adjusting for the chemotherapy regimen. These variables were also independent predictors of the time in days to the onset of OM, after controlling for chemotherapy. On Cox regression analysis, the hazard ratios of a history of OM and anxiety were 1.90 (95% CI, 1.01-3.59, P=0.04) and 1.27 (95% CI, 1.18-1.37, P<0.001), respectively. The hazard ratios of grade 1-2 and 3-4 neutropaenia were 1.86 (95% CI, 1.08-3.07, P<0.01) and 3.08 (95% CI, 2.27-6.40, P<0.01), respectively.

Oral mucositis and its related activity limitations

The incidence of a maximum MTS-activity limitations score of 2 (non-severe limitations) and

TABLE 2 Factors associated with oral mucositis (OM)

Factors	Absence of OM (mouth and throat soreness [MTS] score of<2) [n=83]	Presence of OM (MTS score of ≥2) [n=57]	Bivariate analysis (unadjusted OR [95% CI])	P value	Multivariate binary logistic analysis* (adjusted OR [95% CI])	P value
Patient-related						
Age (years) [No. (%) of patients]						
6-12	43 (51.8)	32 (56.1)	1.0 (reference)	0.614	-	-
13-18	40 (48.2)	25 (43.9)	0.84 (0.43-1.65)			
Gender (No. [%] of patients)						
Male	53 (63.9)	35 (61.4)	1.0 (reference)	0.768	-	-
Female	30 (36.1)	22 (38.6)	1.11 (0.55-2.23)			
Cancer diagnosis (No. [%] of patients)						
Solid tumours	42 (50.6)	20 (35.1)	1.0 (reference)			
Haematological malignancies	41 (49.4)	37 (64.9)	1.90 (0.95-3.8)	0.069	-	-
A history of OM (No. [%] of patients)						
No	51 (61.4)	25 (43.9)	1.0 (reference)	0.040	3.94 (1.49-10.39)	0.006
Yes	32 (38.6)	32 (56.1)	2.04 (1.03-4.05)			
Multivariate ordinal logistic analysis to predict area under the curve (AUC) MTS groups					2.43 (1.14-5.18)	0.02
Cox proportional hazards regression analysis to predict the days to onset of OM (hazard ratio [95% CI])					1.90 (1.01-3.59)	0.04
No. of tooth brushing per day in the first 5 days (mean±SD [range])	1.34±0.6 (1.20-1.48)	1.46±0.6 (1.28-1.63)	1.35 (0.78-2.31)	0.282		
No. of saline rinsing per day in the first 5 days (mean±SD [range])	0.98±1.3 (0.69-1.30)	1.23±1.4 (0.86-1.60)	1.15 (0.90-1.47)	0.278		
Days of sweet food consumption in the first 5 days (mean±SD [range])	1.86±1.7 (1.49-2.22)	1.46±1.6 (1.04-1.87)	0.86 (0.69-1.06)	0.155	-	-
Days of traditional Chinese medicine consumption in the first days (mean±SD [range])	0	0	-			
Anxiety level (mean±SD [range])	15.48±2.9 (14.84-16.11)	18.18±3.4 (17.29-19.08)	1.33 (1.17-1.51)	<0.001	1.46 (1.23-1.73)	<0.001
Multivariate ordinal logistic analysis to predict AUC MTS groups					1.37 (1.20-1.55)	<0.001
Cox proportional hazards regression analysis to predict the days to onset of OM (hazard ratio [95% CI])					1.27 (1.18-1.37)	<0.001
Treatment-related						
Cancer regimen (No. [%] of patients)						
Etoposide-based regimen	15 (18.1)	3 (5.3)	0.29 (0.07-1.21)	0.091	0.28 (0.05-1.54)	0.143
Methotrexate-based regimen	11 (13.3)	14 (24.6)	1.86 (0.65-5.36)	0.251	1.80 (0.44-7.27)	0.412
Cytarabine-based regimen	9 (10.8)	4 (7.0)	0.65 (0.17-2.56)	0.538	0.34 (0.05-2.52)	0.288
Adriamycin-based regimen	22 (26.5)	17 (29.8)	1.13 (0.44-2.91)	0.801	0.89 (0.24-3.21)	0.853
Other anthracyclines-based regimen	7 (8.4)	6 (10.5)	1.25 (0.34-4.59)	0.734	2.31 (0.39-13.57)	0.355
Combined etoposide, methotrexate, cytarabine and/or adriamycin regimen	19 (22.9)	13 (22.8)	1.0 (reference)			
Neutropaenia (109/L) [No. (%) of patients]						
Grade 0 (≥2)	54 (65.1)	11 (19.3)	1.0 (reference)			
Grade 1-2 (1-1.9)	9 (10.8)	16 (28.1)	3.74 (1.75-8.01)	0.001	4.59 (1.81-11.66)	0.001
Grade 3-4 (<0.5-0.9)	20 (24.1)	30 (52.6)	6.24 (1.87-20.79)	0.003	9.19 (1.83-46.29)	0.007
Multivariate ordinal logistic analysis for grade 1-2 neutropaenia to predict AUC MTS groups					2.93 (1.41-6.10)	0.004
Multivariate ordinal logistic analysis for grade 3-4 neutropaenia to predict AUC MTS groups					8.69 (2.12-35.69)	0.003
Cox proportional hazards regression analysis for grade 1-2 neutropaenia to predict the days to onset of OM (hazard ratio [95% CI])					1.86 (1.08-3.07)	<0.01
Cox proportional hazards regression analysis for grade 3-4 neutropaenia to predict the days to onset of OM (hazard ratio [95% CI])					3.08 (2.27-6.40)	<0.01
Liver toxicity (IU/L) [No. (%) of patients]						
Grade 0 (≤1.25)	37 (44.6)	8 (14.0)	1.0 (reference)			
Grade 1-2 (1.26-5)	37 (44.6)	34 (59.6)	4.25 (1.74-10.40)	0.002	-	-
Grade 3-4 (5.1- >10)	9 (10.8)	15 (26.3)	7.71 (2.50-23.76)	<0.001	-	-
Renal toxicity (μmol/L) [No. (%) of patients]						
Grade 0 (≤1.25 x10^6)	83 (100)	57 (100)	Not estimable	-		
Acute emetogenicity [No. (%) of patients]						
Day 1						
Grade 0 (without nausea & vomiting)	59 (71.1)	40 (70.2)	1.0 (reference)			
Grade 1-2 (nausea only to vomiting 1-5 episodes/day)	23 (27.7)	17 (29.8)	1.09 (0.52-2.30)	0.820		
Grade 3-4 (vomiting ≥6->10 episodes/day)	1 (1.2)	0	0	1.00		
Day 2						
Grade 0 (without nausea & vomiting)	53 (63.9)	40 (70.2)	1.0 (reference)			
Grade 1-2 (nausea only to vomiting 1-5 episodes/day)	25 (30.1)	14 (24.6)	1.26 (0.28-5.58)	0.763		
Grade 3-4 (vomiting ≥6->10 episodes/day)	5 (6.0)	3 (5.3)	0.93 (0.19-4.50)	0.932		
Use of cytokine anytime in the first 5 days (No. [%] of patients)						
No	81 (97.6)	56 (98.2)	1.0 (reference)	0.793	-	-
Yes	2 (2.4)	1 (1.8)	0.72 (0.06-8.17)			

* Likelihood ratio test for the overall model (Chi-square=56.48, P<0.001)

a maximum MTS-activity limitations score of 3-4 (severe limitations) in swallowing, drinking, eating, speaking, and sleeping resulting from OM ranged from 18% (n=25) to 35% (n=49). Approximately 39% (22 out of 57) of paediatric patients with OM reported at least two simultaneous non-severe or severe activity limitations, and 25% (14 out of 57) reported having all five non-severe or severe activity limitations resulting from OM simultaneously. Between 64% and 80% (n=16-20) of paediatric patients with severe OM reported severe oral activity limitations. The presence of severe sleeping problems resulting from OM was reported in 60% (n=15) of paediatric patients with severe OM.

Oral mucositis and quality of life

All OMQoL subscale scores of paediatric patients with an AUC MTS of ≥12 were significantly lower than those with an AUC MTS of 0 or 1-11.5 at all the time points (P<0.001). All OMQoL subscale scores of all three AUC MTS subgroups varied significantly between days 1, 7, and 21 (P<0.001). Of those with an AUC MTS of ≥12, 41% (n=19) to 85% (n=39) had a drop in the OMQoL subscale scores to at least 10 points from the baseline, respectively.

Oral mucositis and clinical outcomes

A weight loss of ≥2 kg was common among paediatric patients with a maximum MTS of 3-4 (30%, n=7) or an AUC MTS of ≥12 (21%, n=9) [Table 3]. The mean weight loss increased with increasing maximum MTS or AUC MTS score, reaching a mean loss of 1.64 (SD, 0.5) kg and 1.50 (SD, 1.0) kg in paediatric patients with a maximum MTS of 3-4 and AUC MTS of ≥12, respectively. In addition, for paediatric patients with a maximum MTS of 3-4 or AUC MTS of ≥12, fluid replacement, analgesic use, and oral or intravenous antibiotics were more common (P<0.001). Fever also increased with increasing maximum MTS or AUC MTS scores. No difference was observed for oral or systemic infections among the subgroups. None of the paediatric patients had dose modification, dose delay, or hospitalisation due to OM.

Discussion

The incidence of OM in paediatric patients receiving chemotherapy was moderately high (41%). Factors significantly associated with an increased incidence, early onset, and severe OM included a history of OM, severe neutropaenia, and a high anxiety level; this relationship was independent of the type of chemotherapy. These factors may play a role in the aetiology of OM in a synergistic manner, reflecting the multifactorial nature of OM. The higher ORs of neutropaenia suggest that it may be the most important risk factor. This finding is consistent with our understanding of indirect cytotoxicity and the biological process involved in the pathogenesis of OM.[2] 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.[3] In

TABLE 3. Relationship between the severity of oral mucositis (OM) and clinical outcomes

Variable	Absence of mucositis	Presence of mucositis		P value	Area under curve (AUC) MTS			P value
	Mouth and throat soreness (MTS) score of ≤1 (n=83)	MTS score of 2 (n=32)	MTS score of 3-4 (n=25)		0 (n=55)	1-11.5 (n=39)	≥12 (n=46)	
Weight loss of ≥2kg (n=90)								
No. (%) of patients	5 (13.2)	5 (17.9)	7 (30.4)	0.246	1 (5.0)	7 (25.9)	9 (21.4)	0.171
Mean±SD (range)*	0.63±1.4 (0.17-1.09)	1.30±0.9 (0.95-1.65)	1.64±0.5 (1.41-1.87)	0.002	-0.16±1.4 (-0.81-0.49)	1.44±0.6 (1.27-1.62)	1.50±1.0 (1.09-1.91)	<0.001
Supportive care (No. [%] of patients)								
Fluid replacement (n=137)	30 (37.5)	16 (50.0)	22 (88.0)	<0.001	12 (21.8)	21 (53.8)	35 (76.1)	<0.01
Oral or intravenous antibiotics (n=129)	54 (68.4)	21 (75.0)	20 (90.9)	0.103	33 (62.3)	24 (68.6)	38 (92.7)	0.003
Use of analgesics	2 (2.4)	20 (62.5)	21 (84.0)	<0.001	1 (1.8)	9 (23.1)	33 (71.7)	<0.001
Hospitalisation for OM	0	0	0	-	0	0	0	-
Associated conditions (No. [%] of patients)								
Dose delay	0	0	0	-	0	0	0	-
Dose modification	0	0	0	-	0	0	0	-
Fever (n=139)	21 (25.0)	9 (28.0)	18 (72.0)	<0.001	10 (18.2)	15 (39.5)	23 (50.0)	0.003
Oral or systemic infections (n=139)	5 (6.1)	2 (6.2)	5 (20.0)	0.130	2 (3.6)	4 (10.5)	6 (13.0)	0.218

* Post-hoc comparisons of mean weight loss: MTS scores of 3-4 and 2 were significantly higher than MTS score of ≤1, whereas AUC MTS of ≥12 and 1-11.5 were significantly higher than AUC MTS of 0

addition, neutropaenic patients are at increased risk for microbial colonisation of damaged mucosal surfaces, resulting in increased pro-inflammatory cytokines in oral mucosa, which may aggravate OM.[2] Nevertheless, neutropaenia is largely non-modifiable and therefore there is limited opportunity to intervene in the aetiopathophysiological process and the development of OM and thus limited direct clinical value in this finding. Consequently, routine assessment of neutrophil level prior to commencement of chemotherapy for high-risk groups is important for aggressive prophylactic OM intervention and treatment, or to consider adjustments to the target dosage of chemotherapy to prevent the occurrence and severity of OM.

The independent effect of a history of OM is plausible, considering the genetic susceptibility factors in the inflammatory response which influences cytokine expression and the mucosal ulcerative process, and hence individual predisposition to OM in each cycle of chemotherapy, but this risk factor is non-modifiable. Nevertheless, this association warrants further studies. Our findings suggested that an increased anxiety level was a risk factor for OM. It is probable that oral immunologic function and pro-inflammatory cytokine levels are influenced by anxiety.[4] Avoidance of this risk factor by psycho-educational or cognitive-behavioural intervention may allay some of the increase in incidence and severity of OM. In this study, we did not observe an independent effect of peak liver toxicity on OM in the final model, despite univariate associations. Age, gender, creatinine value, acute emetogenicity, and use of growth factor were not significantly associated with OM, nor were oral care, sweet food, or traditional Chinese medicine consumption.

The prevalence of a multitude of co-existing oral functional limitations reported by paediatric patients with OM was 39%, suggesting that OM is a symptomatic and comorbid condition.[5] Eating and swallowing difficulties were the most severe oral functional limitations during OM, probably related to the potentially compromised muscular movement during swallowing, resulting from mouth and throat soreness, which made eating and swallowing unpleasant. Severe sleeping problems resulting from OM were reported in 60% of paediatric patients with severe OM. The mechanism by which OM influences patients' sleeping is possibly due to intense mouth/throat pain and drooling.

Most paediatric patients with severe OM recorded a drop in the OMQoL subscale scores to at least 10 points from the baseline. The reduction in body weight associated with OM was significant, probably owing to decreased intake and nutritional deficiencies resulting from mouth/throat pain and difficulty in swallowing. In addition, fluid replacement, analgesic usage, and the administration of oral or intravenous antibiotics were significantly associated with severe OM. Contributing to the increased use of fluid replacement and analgesics in patients with severe OM is the combination of pain and oral symptoms that compromise muscular movement, making chewing and swallowing difficult and unpleasant, and thereby reducing patients' will and desire to eat and drink. Fever also increased with an increasing severity of OM; such an association may be attributed to neutropaenia and infections.

Conclusions

Paediatric patients who are neutropaenic, with a history of OM, or with high levels of anxiety have a higher incidence of OM, an earlier onset, and more severe OM. They often suffer a multitude of intense and debilitating impairments of oral function, and sleeping difficulties.

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