DOI: 10.1111/j.1365-263X.2011.01113.x

INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY

Determinants of severe oral mucositis in paediatric cancer patients: a prospective study

NAÏMA OTMANI[1], RAOUF ALAMI[2], LAÏLA HESSISSEN[1], ABDELRHANI MOKHTARI[3], ABDELMAJID SOULAYMANI[3] & MOHAMMED KHATTAB[1]

[1]Pediatric Hemato-Oncology Unit, Children Hospital, Rabat, Morocco, [2]Centre National de Transfusion Sanguine, Rabat, Morocco, and [3]Laboratory of Genetics and Biometry, Ibn Tofaïl University, Kenitra, Morocco

International Journal of Paediatric Dentistry 2011; 21: 210–216

Objective. To analyse the incidence and the determinants of severe oral mucositis (OM) in young cancer patients treated by standard chemotherapy.
Methods. The study was carried out at the Pediatric Hemato-Oncology unit of Children's Hospital of Rabat. Patients under 16 years of age with malignant disease treated by chemotherapy between January 2001 and December 2006 were recorded.
Results. Consecutive patients (n = 970) with malignant disease were studied. The age ranges from 2 months to 16 years (mean, 6.8 ± 4.1 years). OM occurred in 540 (55.6%) patients, and 17.9% of them encountered severe grades. Mean time to onset of the lesions was 10.5 ± 6.8 (range, 1–22 days) and mean duration was 6.8 ± 3.1 (range, 2–23 days). All chemotherapeutic protocols were associated with OM development (range, 20–100%). Patients with severe OM were more likely to have undifferentiated carcinoma of nasopharyngeal type (RR = 2.6, 95% IC 1.1–6.1), non-Hodgkin lymphoma (RR = 2.1, 95% CI 1.2–2.4) and acute leukaemia (RR = 1.7, 95% CI 1.5–3.6). Methotrexate-based therapies were also associated with the worsening of OM (RR = 1.7, 95% IC 1.2–2.6).
Conclusion. Underlying disease and chemotherapy regimens are the principal risk factors of OM development. This model can help in the identification of patients at risk for adequate preventive and therapeutic measures.

Introduction

Oral mucositis (OM) is a common adverse effect of cancer treatments resulting from damage to epithelial cells lining the oral cavity[1]. This related-anticancer secondary effect has been reported to affect 40% of patients receiving standard-dose chemotherapy and exceed 60% of patients receiving conditioning treatment[2,3]. Clinical symptoms range from soreness and mild mucosal erythema to widespread ulceration[4,5]. The latter is associated with intractable pain that may cause marked disruption of the patient's quality of life and can compromise cancer treatment by necessitating drug dose modifications, treatment breaks or treatment cessation[4,6]. The morbidity of mucositis in affected patients is significant and occurrence of moderate–severe OM has been associated with increased number of hospital days, parenteral nutrition, need for narcotic analgesia and mortality[7].

Recent development in mucositis research indicates that multiple factors contribute to mucosal injury. Mucositis is the result of a pathological process to which treatment-induced and patient-related factors contribute[8,9]. Factors such as gender, age, nutritional status, oral microbial environment, and salivary function have been associated with either increased or decreased severity of OM[10–12]. Differences in the severity of mucositis among patients treated with the same chemotherapy regimens were related to the genetic predisposition for mucotoxicity[13]. Despite all these findings, the full spectrum of pathogenesis and the exact risk factors of the disease are still poorly understood, especially in the paediatric cancer population where only few studies are undertaken. The use of busulfan in children receiving alkylant chemotherapy before autologous haematopoietic stem cell transplant was associated with

Correspondence to:
N. Otmani, DDS-MS, Pediatric Hemato-Oncology Unit, Children Hospital, Rabat, 10,000, Morocco.
E-mail: onaima2000@yahoo.fr

increased risk of OM[14]. Rask *et al.*[15] found severe OM significantly related to a high plasma MTX concentration at 28 h after starting the infusion. A recent study by Cheng[16] confirmed the association between the methotrexate-induced stomatotoxicity and the plasma methotrexate concentration at 66 h as well as the level of chemotherapy-induced nausea and emesis (CINV). Another study of Cheng *et al.*[17] suggest that low body weight prior to chemotherapy, neutropenia, and altered liver and renal function during chemotherapy are determinants in the aetiology of OM in children. Other studies[11,12] support that pre-existing oral condition and degree of oral hygiene play a role in the development of OM. Recently, we demonstrated for the first time a relationship between ABO blood group antigens and OM occurrence. The risk of OM was two times higher in patients with blood group O compared to patients with blood group A and blood group B[18].

In this research, we conducted a large prospective study to determine the incidence, risk factors and causes of OM in young cancer patients; notably regarding variations across chemotherapy regimens and type of cancer. This will help greatly in identification of patients at risk for a better implementation of therapeutic approaches.

Methods

This prospective cohort study was conducted at the Pediatric Hemato-Oncology Unit of Children's Hospital of Rabat between January 2001 and December 2006. Nine hundred and seventy patients under 16 years and scheduled to receive chemotherapy during this period were enrolled. Exclusion criteria were: (i) previous chemotherapy, (ii) radiation therapy affecting the salivary glands, (iii) children with other disease than malignancies, and (iv) presence of oral abnormalities at baseline corresponding to WHO scale grade ≥1.

Demographic and clinical data including age, gender, body surface area (BSA), underlying disease, and type and dosage of chemotherapy were collected from patients' medical records. Baseline interviews and oral examination were conducted systematically in all patients before the administration of chemotherapy. Buccodental exploration and follow-up were performed by the same assessor (dentist who had received training on using the chosen scoring system) in all patients with the purpose of reducing any possible subjectivity. Then children and their parents, who are their primary care givers, were instructed to maintain oral health practices and to perform three times a day a mouthwash with a solution of water and sodium bicarbonate. Adjunction of topical Amphotericin B was added if necessary in patients with high risk of candidiasis (according to our unit practices).

On every hospitalization or outpatient visit, patients meet the medical staff and are referred to the dental practitioner when there are oral complaints or soreness. WHO scale was used[19] for grading OM: grade 0 = none; grade 1 = soreness and erythema; grade 2 = painful ulceration, ability to eat solids; grade 3 = painful ulceration, requires liquid diet; and grade 4 = alimentation not possible, requires parenteral support. Moderate OM grade was designed as the WHO grade 1–2 and severe OM grade as the WHO grade 3–4. Haematological toxicity was also recorded with neutropenia defined as absolute neutrophil count (ANC) $<1000/mm^3$ and severe neutropenia as ANC $<500/mm^3$.

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 10.0 (SPSS, Inc., Chicago, IL, USA). Data were summarised using descriptive statistics. Where appropriate, a chi-squared test and the Fisher's exact test were used to investigate the relationship between two specific variables. Multivariate analysis was used to estimate the risk of severe OM versus no/moderate OM. Statistical significance was defined by $P \leq 0.05$.

Results

Study population

From January 2001 and December 2006, 970 consecutive patients at the Pediatric Hemato-Oncology Unit of Children's Hospital of Rabat were studied. Six hundred and ten (62.8%)

Table 1. Baseline characteristics of the patients studied.

Parameters	All patients *n* = 970	Patients with no mucositis *n* = 430	Patients with mucositis *n* = 540	*P*-value
Age years, mean ± SD	6.8 ± 4.1	6.7 ± 4.1	6.8 ± 4.1	0.38
Gender, male/female (%)	619/351 (63.8/36.2)	288/142 (46.5/40.4)	331/209 (34.1/21.5)	0.06
BSA (m^2), mean ± SD	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.3	0.95
Underlying disease *n* (%)				
Haematological malignancies	610	245 (40.2)	365 (59.8)	<0.0001
Acute leukaemia	318	108 (33.9)	210 (66.1)	
Non-Hodgkin lymphoma	202	71 (35.2)	131 (64.8)	
Hodgkin lymphoma	90	66 (73.4)	24 (26.6)	
Solid tumours	360	185 (51.4)	175 (48.6)	
Renal tumours	95	61 (64.3)	34 (35.7)	
Neuroblastoma	72	28 (38.9)	44 (61.1)	
Bone tumours	70	41 (58.5)	29 (41.5)	
Soft tissue sarcoma	48	18 (37.5)	30 (62.5)	
Retinoblastoma	30	14 (46.6)	16 (53.4)	
UCNT	25	11 (44)	14 (56)	
Hepatic tumours	7	6 (85.7)	1 (14.3)	
Teratoma	8	4 (50)	4 (50)	
Other	5	2 (40)	3 (60)	
ANC, median (IQR) cells/mm3	–	–	414 (100–1472.5)	–
Onset (days), mean ± SD (range)	–	–	10.5 ± 6.8 (1–22)	–
Duration (days), mean ± SD (range)	–	–	6.8 ± 3.1 (2–23)	–

were diagnosed with haematological malignancies, and 360 (37.2%) with solid tumours. There were 619 males (63.8%) and 351 females (36.2%). The mean age ± SD was 6.8 ± 4.1 years (range, 2 months–16 years), and the mean BSA ± SD was 0.8 ± 0.3 at the time of diagnosis (Table 1).

Incidence of oral mucositis

Oral mucositis was experienced by 540 patients (55.6%). On average, OM tends to occur on day 10.5 ± 6.8 after the start of chemotherapy (range, 1–22 days) and to resolve on day 6.8 ± 3.1 (range, 2–23 days). More than 67% of patients with OM showed concomitant neutropenia with severe neutropenia (ANC <500/mm^3) occurring in 51.4% of the cases.

Patients with acute leukaemia and non-Hodgkin lymphoma developed OM in 66.1% and 64.8%, respectively. In the setting of solid tumours, patients with soft tissue sarcoma and neuroblastoma showed the higher proportion of OM with 62.5% and 61.1%, respectively.

Patients with haematological malignancies experienced more OM (59.8%) than those with solid tumours (48.6%) ($P < 0.0001$). No significant relationship was found between OM occurrence and sex, age and body surface area (BSA) ($P > 0.05$).

All chemotherapeutic regimens were associated with expression of OM (Table 2). In patients with haematological malignancies, treatments for acute myeloid leukaemia showed the highest incidence of OM: 83.3% with AMLMA protocol, and 71.4% with VIC protocol. Patients with acute lymphoblastic leukaemia developed OM in 61.4% and 62.1%, respectively, for Frall and Marall regimens. Regimens for non-Hodgkin lymphomas showed an incidence of 74.1% with LMB protocol and 68% with LMT protocol. In the setting of solid tumours, the highest incidence of OM was showed in CEV-IVE protocol (100%) and VAC-VAD protocol (69.2%), used for soft tissue sarcoma.

Determinants of severe OM

Of the 540 patients with OM, 366 (67.7%) developed moderate OM (WHO Grade 1–2), and 174 (32.3%) developed severe OM (WHO Grade 3–4). Patients with haematological malignancies were more prone to develop severe grades than those with solid tumours (RR = 2.3, 95% IC 1.5–3.4). Children with

Table 2. Chemotherapy protocols and OM incidence.

Regimen by type of disease	All patients	Patients with mucositis
Acute lymphoblastic leukaemia		
Frall	122	75 (61.4)
Marall	119	74 (62.1)
Acute myeloblastic leukaemia		
VIC	35	25 (71.4)
AMLMA	42	35 (83.3)
Non-Hodgkin B lymphoma		
GFALB	65	31 (47.7)
LMB	108	80 (74.1)
Non-Hodgkin T lymphoma		
LMT	25	17 (68)
Anaplastic lymphoma		
ALCL	5	3 (60)
Hodgkin lymphoma		
ABVP-COPP	22	7 (31.8)
OPPA-COPP	51	12 (23.5)
VAMP	5	1 (20)
VBVP	8	2 (25)
Ewing sarcoma		
Memphis	28	8 (28.5)
Osteosarcoma		
Adria-Cispl	33	15 (45.4)
UCNT		
BEC	25	14 (56)
Neuroblastoma		
CO	11	6 (54.5)
CADO/VP16-Cispl	43	24 (55.8)
Retinoblastoma		
CADO/VP16-Cispl	31	16 (51.6)
Soft tissue sarcoma		
CEV-IVE	9	9 (100)
IVA	32	17 (53.1)
VAC-VAD	13	9 (69.2)
Teratoma		
VIP	7	4 (57.1)
VBP	1	–
Hepatoblastoma		
SIOPEL	8	2 (25)
Nephroblastoma		
GFA nephro	91	31 (34.1)
Others	39	23 (58.9)

Values in parentheses are in percentages.

non-Hodgkin lymphoma and acute leukaemia had, respectively, 2.1-fold (95% CI 1.2–2.4) and 1.7-fold (95% CI, 1.5–3.6) increase in risk of developing severe OM (Table 3). Among patients with solid tumours, those with undifferentiated carcinoma of nasopharyngeal type (UCNT) were more likely to experience severe OM (RR = 2.6, 95% IC 1.1–6.1). Of the different chemotherapy agents, methotrexate (RR = 1.7, 95% IC 1.2–2.6) was the only molecule associated with the worsening of OM in this patient population.

Discussion

The present prospective study, in which a great number of patients with a variety haematological malignancies and solid tumours have been included, showed that OM is a substantial clinical problem in young cancer patients. OM was experienced by 55.6% of our patients and 17.9% of them encountered severe OM. This incidence was similar to that referred by Herlofson *et al.*[20], but was lower than that reported by Bonnaure-Mallet *et al.*[12] and Fayle and Curzon[21] where the incidence approximates 80%. Similar to previous reports[22], OM occurred during the second week after chemotherapy infusion and the majority of patients (98.3%) showed resolution on or before 2 weeks.

In agreement with earlier reports[11,17], no association was found between OM grades and age or gender in paediatric patients; whereas studies in adults have found that female patients are more susceptible to the development of mucositis[23]. On the other hand, we could not establish an association between the BSA prior to chemotherapy and severity of OM, although this factor was proposed as determinant in mucositis occurrence by other studies[10,17].

Conflicting data exist regarding the relationship between the type of the malignancy and OM development. Although some studies consider mucositis not to be directly related to a specific malignant disease[11,24], others have suggested that the type of cancer affect the OM worsening[3,14,25]. According to the results of Martino *et al.*[26], we found that patients with haematological malignancies are at higher risk of developing severe OM than those with solid tumours. Similar to the study of Vera-Llonch *et al.*[27] we identified patients with undifferentiated carcinoma of nasopharyngeal type (UCNT) as a population at risk of high grades OM.

It is generally agreed that chemotherapeutic agents are the most important factor influencing the susceptibility to OM. In the young population, the incidence rate of OM was increased with methotrexate therapies[15,16]. Regimens combining an alkylating agent, anthracycline, a vinca-alkaloid, and metho-

Table 3. Severity of OM according to selected characteristics.

Parameters	Moderate OM *n* = 366 (67.7%)	Severe OM *n* = 174 (32.3%)	RR (95% IC) Severe *vs* no/mild OM	*P*
Underlying disease *n* (%)				
Haematological malignancies	230 (63.1)	135 (36.9)	2.3 (1.5–3.4)	<0.0001
Acute leukaemia	135 (64.3)	75 (35.7)	1.7 (1.2–2.4)	0.001
Non-Hodgkin lymphoma	75 (57.2)	56 (42.8)	2.1 (1.4–3.0)	<0.0001
Hodgkin lymphoma	20 (83.3)	4 (16.4)	0.1 (0.06–0.5)	<0.0001
Solid tumours	136 (77.7)	39 (22.3)	0.4 (0.2–0.6)	<0.0001
Renal tumours	29 (85.3)	5 (14.7)	0.2 (0.09–0.5)	0.001
Neuroblastoma	37 (84.1)	7 (15.9)	0.4 (0.2–1.0	0.05
Bone tumours	26 (89.6)	3 (10.3)	0.1 (0.05–0.6)	0.001
Soft tissue sarcoma	21 (70)	9 (30)	1.0 (0.5–2.2)	0.88
Retinoblastoma	12 (75)	4 (25)	0.6 (0.2–2.0)	0.63
UCNT	5 (35.7)	9 (64.3)	2.6 (1.1–6.1)	0.01
Hepatic tumours	1 (100)	–	–	–
Teratoma	3 (75)	1 (25)	0.6 (0.08–5.3)	1.00
Other	2 (66.6)	1 (33.4)	1.5 (0.1–11.7)	0.54
Cytotoxic agents (%)				
Cisplatin–Carboplatin	39 (65)	21 (35)	0.9 (0.5–1.5)	0.72
Vincristine	214 (71.6)	85 (28.4)	0.7 (0.5–1.1)	0.17
Daunorubicin–Doxorubicin	174 (69.9)	75 (30.1)	0.6 (0.4–0.9)	0.02
Methotrexate	127 (65.8)	66 (34.2)	1.7 (1.2–2.6)	0.002
Cytarabine	84 (67.2)	41 (32.4)	1.0 (0.6–1.5)	0.82
Etoposide	30 (71.4)	12 (28.6)	0.4 (0.2–0.8)	0.007
CPM	105 (69.1)	47 (30.9)	0.6 (0.4–0.9)	0.03
Ifosfamide	18 (81.8)	4 (18.2)	0.4 (0.1–1.4)	0.18
Bleomycin	9 (50)	9 (50)	1.1 (0.5–2.5)	0.64
Actinomycin-D	31 (81.6)	7 (18.4)	0.6 (0.2–1.4)	0.24
6-mercaptopurine	36 (63.2)	21 (36.8)	1.2 (0.7–2.0)	0.48
Vinblastine	5 (83.3)	1 (16.7)	0.2 (0.03–1.6)	0.15
Asparaginase	47 (74.6)	16 (25.4)	0.5 (0.3–1.0)	0.04

trexate (MTX) or etoposide were also associated with a very high rate of severe mucositis in children[28]. In this study, treatment with CEV-IVE regimen used in soft tissue sarcoma and AMLMA regimen used in acute myeloid leukaemia were associated with the highest incidence of OM. Mucosal toxicity was also increased in non-Hodgkin lymphoma patients treated by LMB and LMT protocols, and in those with acute lymphoblastic leukaemia treated by Frall or Marall protocols. Methotrexate therapies were found independent risk factors for worsening mucositis. Antimetabolites have already been associated with OM in our previous report[18]. These drugs which are S-phase-specific agents have a direct toxic effect on rapidly dividing oral mucosal cells, resulting in inflammation and epithelial damage[4]. The excretion of these drugs into the saliva may contribute to the development of such lesions[29].

Despite the availability of many therapeutic agents that claim to prevent or reduce OM severity, there has been no clear-cut standard of care defined to prevent severe mucositis in young patients. The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) guidelines recommend implementation of good oral hygiene practices prior to commencing cancer therapy[2,30]. Pain control and nutritional support are also required. Until more evidence-based guidelines are available, more research based on the analysis of the different factors that interact in mucositis pathogenesis is needed.

Conclusion

This study with a large sample size and a broad representation of patients gives more insights about patterns and determinants of chemotherapy-induced OM in children. Results confirmed that OM is a widespread and serious problem among children with cancer, and showed the greater risk of severe

OM in patients with acute leukaemia, non-Hodgkin lymphoma, undifferentiated carcinoma of nasopharyngeal type and in those under methotrexate-based regimens. This model may help in the development of novel preventive and therapeutic modalities designed specifically for these patients.

What this paper adds

- Oral mucositis is a substantial clinical problem in young cancer patients.
- Patients with haematological malignancies are more prone to develop oral mucositis than those with solid tumours.
- Patients with undifferentiated carcinoma of nasopharyngeal type, non-Hodgkin lymphoma and acute leukaemia are at higher risk of severe oral mucositis.

Why this paper is important to paediatric dentists

- The study showed the incidence of OM in a variety of malignancies and chemotherapy protocols.
- This model can help in identification of patients at risk for adequate preventive and therapeutic measures.

References

1 Sonis ST, Elting LS, Keefe D *et al.* Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology and consequences for patients. *Cancer* 2004; **100**: 1995–2025.

2 Rubenstein EB, Peterson DE, Schubert M *et al.* Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004; **100**: 2026–2046.

3 Elting L, Cooksley C, Chambers M, Cantor S, Manzullo E, Rubenstein E. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* 2003; **98**: 1531–1539.

4 Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998; **34**: 39–43.

5 Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer* 2004; **4**: 277–284.

6 Epstein JB, Schubert MM. Oropharyngeal mucositis in cancer therapy. *Oncology* 2003; **17**: 1767–1776.

7 Sonis ST, Oster G, Fuchs H *et al.* Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol* 2001; **19**: 2201–2205.

8 Barasch A, Peterson DF. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. *Oral Oncol* 2003; **39**: 91–100.

9 Anthony L, Bowen J, Garden A, Hewson I, Sonis S. New thoughts on the pathobiology of regimen-related mucosal injury. *Support Care Cancer* 2006; **14**: 516–518.

10 Raber-Durlacher JE, Weijl NI, Abu Saris M, de Koning B, Zwinderman AH, Osanto S. Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. *Support Care Cancer* 2000; **8**: 366–371.

11 Cheng KKF, Mollassiotis A, Chang AM, Wai WC, Cheung SS. Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. *Eur J Cancer* 2001; **37**: 2056–2063.

12 Bonnaure-Mallet M, Bunetel L, Tricot-Doleux S, Guerin J, Bergeron C, LeGall E. Oral complications during treatment of malignant diseases in childhood: effect of tooth brushing. *Eur J Cancer* 1998; **34**: 1588–1591.

13 Robien K, Schubert MM, Bruemmer B, Lloid ME, Potter JD, Ulrich CM. Predictors of oral mucositis in patients receiving hematopoietic cell transplants for chronic myelogenous leukaemia. *J Clin Oncol* 2004; **22**: 1268–1275.

14 Fadda G, Campus G, Luglie P. Risk factors for oral mucositis in paediatric oncology patients receiving alkylant chemotherapy. *BMC Oral Health* 2006; **6**: 13.

15 Rask C, Albertioni F, Bentzen SM, Schroeder H, Peterson C. Clinical and pharmacokinetic risk factors for high-dose methotrexate-induced toxicity in children with acute lymphoblastic leukemia-a logistic regression analysis. *Acta Oncol* 1998; **37**: 277–284.

16 Cheng KKF. Association of plasma methotrexate, neutropenia, hepatic dysfunction, nausea/vomiting and oral mucositis in children with cancer. *Eur J Cancer Care* 2008; **17**: 306–311.

17 Cheng KKF, Goggins WB, Lee VWS, Thompson DR. Risk factors for oral mucositis in children undergoing chemotherapy: a matched case–control study. *Oral Oncol* 2008; **44**: 1019–1025.

18 Otmani N, Alami R, Soulaymani A, El Mokhtari A, Khattab M. Sex, age and ABO blood groups in chemotherapy-induced oropharyngeal mucositis. *Minerva Stomatol* 2008; **57**: 505–509.

19 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results in cancer patients. *Cancer* 1991; **47**: 207–214.

20 Herlofson BB, Norman-Pederson k, Redfors M, Fossa SD. Oral mucosa side effects of cytotoxic chemotherapy of testicular cancer. *Eur J Oral Sci* 1997; **105**: 523–526.

21 Fayle SA, Curzon MEJ. Oral complications in pediatric oncology patients. *Pediatr Dent* 1991; **13**: 289–295.

22 Ramirez-Amador V, esquivel-Pedraza L, Hoùar A *et al.* Chemotherapy associated oral mucosal lesions in patients with leukaemia or lymphoma. *Eur J Cancer* 1996; **32**: 322–327.

23 Sloan JA, Loprinzi CL, Novotny PJ, Okuno S, Nair S, Barton DL. Sex differences in fluorouracil-induced stomatitis. *J Clin Oncol* 2000; **18**: 412–420.

24 Blijlevens N, Schwenkglenks M, Bacon P *et al.* Prospective oral mucositis audit: oral mucositis in

patients receiving high-dose melphalan or BEAM conditioning chemotherapy-European Blood and Marrow Transplantation Mucositis Advisory Group. *J Clin Oncol* 2008; **26**: 1519–1525.
25 Bolwell BJ, Kalaycio M, Sobecks R *et al.* A multivariable analysis of factors influencing mucositis after autologous progenitor cell transplantation. *Bone Marrow Transplant* 2002; **30**: 587–591.
26 Martino M, Morabito E, Console G *et al.* Differences in transplant-related complications between hematologic malignancies and solid tumors receiving high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Tumori* 2003; **89**: 385–390.
27 Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer* 2006; **106**: 329–336.
28 Gandemer V, Le Deley MC, Dollfus C *et al.* Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. *J Pediatr Hematol Oncol* 2007; **29**: 86–94.
29 Epstein JB, Tsang AHF, Warkentin D, Ship JA. The role of salivary function in modulating chemotherapy-induced oropharyngeal mucositis: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 39–44.
30 Glenny AM, Gibson F, Auld E *et al.* The development of evidence-based guidelines on mouth care for children, teenagers and young adults treated for cancer. *Eur J Cancer* 2010; **46**(8): 1399–412.