original article

Annals of Oncology 21: 1706–1711, 2010
doi:10.1093/annonc/mdp596
Published online 20 January 2010

Citrulline-based assessment score: first choice for measuring and monitoring intestinal failure after high-dose chemotherapy

A. H. Herbers[1]*, T. Feuth[2], J. P. Donnelly[1] & N. M. Blijlevens[1]

Departments of; [1]Haematology and [2]Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Received 16 June 2009; revised 27 October 2009; accepted 9 December 2009

Background: Currently, objective tests are lacking that enable the extent and duration of intestinal mucosal damage induced by myeloablative chemotherapy to be determined. To address this problem, we explored a citrulline-based assessment score as this amino acid is a simple quantitative marker of intestinal failure.

Patients and methods: From March 2004 to June 2007, citrulline concentrations were determined at baseline and at least once weekly after the start of myeloablative chemotherapy until 30 days thereafter among 94 allogeneic or autologous haematopoietic stem-cell transplant recipients. The patients were divided into three groups according to the regimen they received: (i) carmustine, etoposide, cytarabine and melphalan/high-dose melphalan, (ii) cyclophosphamide and total body irradiation ± antithymocyte globulin and (iii) idarubicin-containing regimens. Intestinal mucosal damage was described either by level of citrulline on each day, on the basis of different thresholds of citrulline indicating the severity of villous atrophy, or by area under the curve using reciprocal value of 10/citrulline.

Results: Regimens that incorporated idarubicin induced the most severe intestinal toxicity. Scores based on the level of citrulline, using severity thresholds, and on the area under the reciprocal curve are able to discriminate between the damage induced by different high-dose chemotherapy regimens.

Conclusion: A citrulline-based assessment score appears objective, validated, reproducible, reliable, specific and sensitive making it a suitable first choice for measuring and monitoring intestinal mucositis.

Key words: chemotherapy, citrulline, mucositis

introduction

Mucositis is a common adverse effect of myeloablative chemotherapy or radiotherapy used to prepare patients for a haematopoietic stem-cell transplant (HSCT) [1]. Patients describe oral mucositis (OM) as the most debilitating complaint though the entire alimentary tract is affected. Clinical consequences of mucositis include dehydration, malnutrition, potentially life threatening infections and possibly even increased mortality [2]. Mucositis can have a direct impact on morbidity—prolonged hospital stay, increased antibiotic usage and the need for parenteral nutrition—and is a serious economic burden [3].

Consequently, early detection, assessment and monitoring of mucosal damage are necessary for effective management. Therefore, ideally, we should have a scoring system that is objective, validated, reproducible, reliable (without interobserver and intraobserver variation), sensitive and precise and requires minimal training as set out by the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) [4].

Most assessment scales for mucosal damage are focussed on OM, since it is easy to recognise. Both the World Health Organization scale and the National Cancer Institute—Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 3.0 scale are commonly used [5, 6]. These combine objective signs of mucositis (erythema and ulcer formation) with subjective and functional outcomes (pain and the ability to eat). Their reliability is dependent on interobserver and intraobserver variation, which can be improved by training [7].

Intestinal mucosal damage presents a different challenge as it cannot be seen or readily detected. Endoscopy with or without biopsy is precluded because of the high likelihood for bleeding complications as mucositis develops contemporaneously with bone marrow aplasia, so patients are also profoundly thrombocytopenic [8]. Certain non-invasive tests such as the sugar permeability tests can detect alterations in permeability due to loss of the epithelial surface but are cumbersome, wholly dependent on patient compliance and cannot distinguish

*Correspondence to: Dr A. H. E. Herbers, Department of Haematology, Radboud University Nijmegen Medical Centre, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands. Tel: +31-24-361-47-62; Fax: +31-24-354-20-80;
E-mail: A.Herbers@hemat.umcn.nl

between mucosal damage induced by different myeloablative regimens [9]. The NCI-CTCAE version 3.0 scale is considered the best scale for intestinal (alimentary) mucositis [10] and is on the basis of signs and symptoms related to gastrointestinal changes, including nausea, vomiting and diarrhoea [5] However, this scale suffers from several drawbacks that include a lack of reliability and validation, as the signs and symptoms are influenced by the use of antiemetics and opioids for analgesia, which induce constipation. Furthermore, the score is neither specific nor objective.

Consequently, the lack of a diagnostic tool to measure intestinal mucositis impedes good clinical management and hampers the development of clinical studies. We and others have explored using the amino acid citrulline as it can be determined in blood and has been shown to be a reliable and objective biochemical marker of small-bowel enterocyte mass [11–16]. Injury to the small intestine after high-dose chemotherapy is characterised by crypt apoptosis, hypoplastic villous atrophy and loss of enterocytes and can be measured by the decline in circulating citrulline with low concentrations corresponding with severe intestinal damage [12, 17]. In patients with small-bowel disease and recipients of an intestinal transplant, citrulline provides an indication of global function and a useful nutritional prognosis [18]. We therefore undertook an observational audit to explore an assessment scale for intestinal mucosal barrier damage on the basis of the levels of circulating citrulline that had been measured in patients who had received a T-cell-depleted allogeneic HSCT or an autologous HSCT to treat a haematological malignancy.

patients and methods

patients

From March 2004 to June 2007, a cohort of 94 patients participated of whom 51 patients had received a T-cell-depleted allogeneic HSCT [including 20 recipients of a voluntary unrelated donor (VUD) transplant] and 43 patients had received an autologous HSCT.

The myeloablative regimens consisted of high-dose melphalan (HDM), carmustine, etoposide, cytarabine and melphalan (BEAM), cyclophosphamide, antithymocyte globulin and total body irradiation (Cy–ATG–TBI), cyclophosphamide and total body irradiation (Cy–TBI), idarubicin, cyclophosphamide and total body irradiation (IDA–Cy–TBI) and idarubicin, busulfan and cyclophosphamide (IDA–Bu–Cy). On admission, all transplant recipients had a central venous catheter inserted. Parenteral nutrition was started during conditioning. Cyclosporine was given to allogeneic HSCT recipients for prophylaxis against graft-versus-host disease (GVHD). Patients were given ondansetron for antiemesis. Haematopoietic growth factors were not used. Antimicrobial prophylaxis and therapy were given according to a standard protocol and consisted of valaciclovir and ciprofloxacin. Agents that might ameliorate alimentary tract mucositis were not given. Renal function was determined to allow for dosage adjustment of melphalan when the creatinine clearance was <30 ml/min and to identify high concentrations of citrulline which increase when creatinine clearance falls <50 ml/min [19]. The glomerular filtration rate (GFR) was estimated thereafter from the serum creatinine using the formula of Cockcroft and Gault [20].

citrulline measurements

Since the myeloablative therapy determines the severity of mucositis [21], plasma was obtained at baseline i.e. before the start of the conditioning regimen and at least once per week after the start of the regimen till 30 days. Plasma was stored at −80°C until required. Citrulline concentrations (μM) were measured by a standard procedure for determining amino acids using high-performance liquid chromatography (Shimadzu, Kyota, Japan) [22].

data analysis

The patients were divided into three groups, according to the myeloablative regimen: group 1, BEAM or HDM; group 2, Cy–TBI ± ATG and group 3, all regimens containing idarubicin.

Citrulline was described in two ways:

- by the level of citrulline on each day [mean ± standard deviation (SD)], on the basis of different thresholds of citrulline. We applied thresholds that indicate severity of villous atrophy documented in patients with coeliac disease, i.e. citrulline level <10 μM is considered predictive of total villous atrophy, citrulline level 10–20 μM is predictive of proximal only total or subtotal villous atrophy and >20 μM indicating only partial villous atrophy [11]. The nadir of each regimen was determined and the duration and frequency of a citrulline <10 μM was calculated.
- by the area under the curve (AUC) using rescaled reciprocal of the citrulline value (10/citrulline) analogous to the analysis reported by Wardley et al. [21], who showed that for OM, myeloablative regimens could be distinguished according to the area under the OM curve.

We modelled the 10/citrulline profile over the first 30 days (or until discharge if this occurred earlier) after the start of conditioning for each patient using linear mixed models treating the 'patient' as a random factor, 'conditioning regimen' as a fixed factor in combination with a six-degree polynomial function of time. Using this modelling approach, we could adequately deal with missing values resulting from only 3 or 4 citrulline measurements per week per patient.

One-way analysis of variance (ANOVA) or the Kruskall–Wallis test was used to compare the three groups with respect to continuous variables. The severity of mucositis was measured in each regimen by depth of citrulline curve (nadir), the duration of citrulline <10 μM and the area under the 10/citrulline curve. In order to develop an assessment scale, we sought to discriminate between the different regimens by using the two different approaches. A P value of <0.05 was considered to indicate significance. SAS version 8.2 software (SAS Institute Inc., Cary, NC) was used for statistical analysis.

results

The mean age of the 94 patients was 49 (range 17–65) years. Group 1 consisted of 40 patients who received an autologous HSCT. Twenty-nine patients were treated for multiple myeloma with HDM. Eleven patients were treated for non-Hodgkin's lymphoma with BEAM. Group 2 consisted of 29 patients who were treated with Cy–TBI ± ATG. Eight received a sibling donor allogeneic HSCT and were treated with Cy–TBI. Twenty-one patients received a VUD transplant and were treated with ATG–Cy–TBI. Group 3 contained 25 patients treated for several haematological diseases with IDA–Bu–Cy or IDA–Cy–TBI preceding a HSCT. Three patients in group 3 received an autologous HSCT and 22 patients an allogeneic HSCT. The demographic data of the HSCT recipients divided into the three groups, according to the myeloablative regimen are summarised in Table 1.

There were no treatment-related deaths and every patient had a GFR >50 ml/min, hence there was no need to adjust the

Table 1. Demographic data of HSCT recipients treated with myeloablative regimens

Group	Conditioning	Doses	Frequency	Days	Type of SCT, day	Number of patients	Male/female	Disease
1	HDM					40	17/12	MM
	Melphalan	100 mg/m^2	od	1, 2	Autologous, day 4			
	BEAM						7/4	NHL
	Carmustine	300 mg/m^2	od	1	Autologous, day 7			
	Etoposide	200 mg/m^2	b.i.d.	2–5				
	Cytarabine	200 mg/m^2	b.i.d.	2–5				
	Melphalan	140 mg/m^2	od	6				
2	Cy–TBI					29	6/2	NHL/CLL (7), MDS/AML (1)
	Cyclophosphamide	60 mg/kg	od	1, 2	Allogeneic, day 7			
	Total body irradiation	4–5 Gy	od	5, 6				
	ATG–Cy–TBI						16/5	NHL/CLL (6), CML (3), MDS/AML (9), ALL (2), myelofibrosis (1)
	Antithymocyte globulin	2 mg/kg	od	1, 2	VUD, day 9			
	Cyclophosphamide	60 mg/kg	od	3, 6				
	Total body irradiation	4–5 Gy	od	7, 8				
3	IDA–Bu–Cy					25	12/2	CML (1), MDS/AML (10), ALL (3)
	Idarubicin	42 mg/m^2	od	1	Allogeneic (12), autologous (2), day 13			
	Busulfan	4 mg/kg	od	7, 8				
	Cyclophosphamide	60 mg/kg	od	11, 12				
	IDA–Cy–TBI						10/1	NHL/CLL (4), MDS/AML (5), ALL (1), Morbus Waldenstrom (1)
	Idarubicin	42 mg/m^2	Over 48 h	1	Allogeneic (10), autologous (1), day 13			
	Cyclophosphamide	60 mg/kg	od	7, 8				
	Total body irradiation	4–5 Gy		11, 12				

HSCT, haematopoietic stem-cell transplant; SCT, stem-cell transplant; od, once daily; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; b.i.d., two times daily; CLL, chronic lymphocytic leukaemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia; VUD, voluntary unrelated donor; ALL, acute lymphocytic leukaemia.

dose of melphalan or to correct citrulline concentrations for renal dysfunction.

The course of observed citrulline means in the three groups is shown in Figure 1. Mean citrulline at start of the conditioning regimen for all patients was 22.1 μM ± 8.1 (mean ± SD). No significant differences were found at baseline between the three groups ($P = 0.276$). A significant decrease was seen in all groups immediately after the start of myeloablative therapy, with citrulline reaching 10 μM around day 9 (group 1: 9.6 ± 3.2, group 2: 8.4 ± 3.3 and group 3: 9.4 ± 4.3). A nadir was reached, respectively, on 14.4 ± 2.6 day for group 1, 15.3 ± 4.7 day for group 2 (disregarding the outlying mean value at day 10, on the basis of a single observation) and 16.5 ± 2.9 day for group 3 (with a significant difference between groups 1 and 3; $P = 0.008$; Mann–Whitney U test). All patients in group 3 had citrulline values <10 μM (reflecting total villous atrophy) for at least one day, compared with 88% (35 of 40 patients) in group 1 and 84% (21 of 25 patients) in group 2. During the first 30 days after the start of the conditioning, patients in group 3 experienced 21 ± 5 days of citrulline <10 μM in comparison with 16 ± 7 days for group 1 and 17 ± 7 days for group 2 (Kruskal–Wallis test; $P = 0.005$).

The conditioning regimens incurring the most severe intestinal mucositis were those that incorporated idarubicin on the basis of the course of citrulline. Group 3 had on average lower citrulline levels starting from day 13 compared with groups 1 and 2, and on the basis of the AUC. The mean area under the modelled 10/citrulline curve of group 3 was 44.7 (day/μM) compared with 32.8 (day/μM) for group 1 and 32.6 (day/μM) for group 2 ($P < 0.0001$, one-way ANOVA) (Figure 2).

discussion

This observational audit shows that the course of citrulline is able to discriminate between different regimens. This makes a score on the basis of citrulline more specific and sensitive than either the NCI-CTCAE assessment score or sugar permeability tests [5, 9]. Citrulline as a marker for the myeloablative regimen-induced intestinal damage is highly reproducible, showing the same course of citrulline for each single patient treated in a certain regimen. Furthermore, citrulline is a quantitative and objective value, lacking interobserver and intraobserver variation [12, 23].

Low citrulline concentrations represent intestinal failure independent of the underlying cause and also correlate with the clinical condition of different diseases including small-bowel disease, villous atrophy diseases, immunodeficiency virus enteropathy or severe intestinal infectious disease [18].

In adult patients with short-bowel syndrome, a citrulline threshold of 20 μM permits the classification into either transient ($n = 20$) or permanent ($n = 37$) chronic intestinal failure, with 92% sensitivity, 90% specificity, 95% positive and 86% negative predictive values, respectively [15]. Almost the

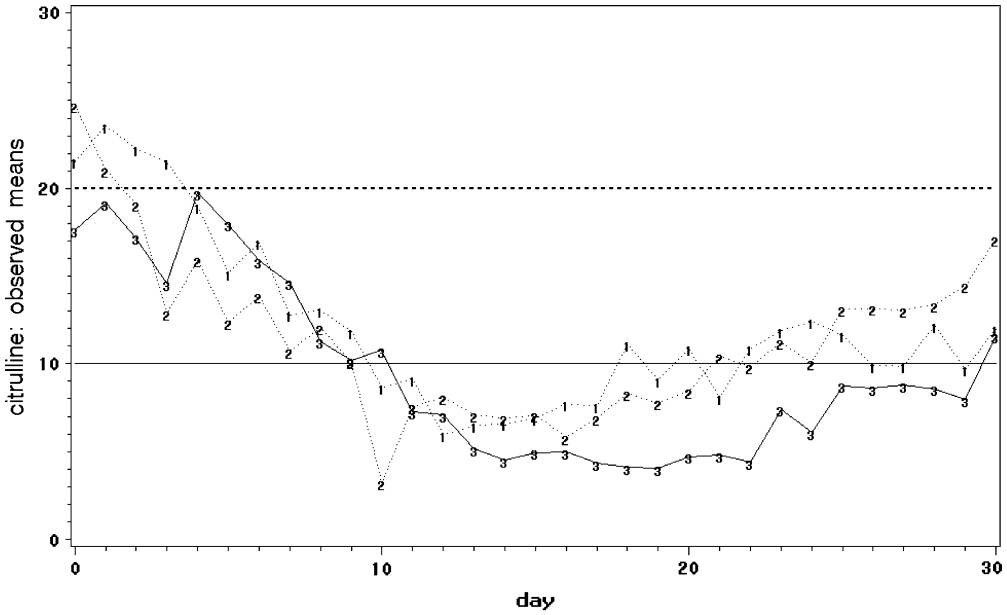

Figure 1. Course of citrulline after the start of the conditioning regimen by the level of citrulline on each day. A significant decrease was seen in all groups immediately after the start of myeloablative therapy, with citrulline reaching 10 μM around day 9. A nadir was reached, respectively, on 14, 15 and 17 days after the start of the conditioning regimen in group 1, 2 and 3. The conditioning regimens incurring the most severe intestinal mucositis were those that incorporated idarubicin (group 3). Group 3 had on average lower citrulline levels starting from day 13. The duration of citrulline <10 μM was 21 days for group 3 and, respectively, 16 and 17 days for group 1 and 2. Vertical axis: observed mean citrulline values in μM. Numbers refer to the groups are 1: carmustine, etoposide, cytarabine and melphalan and high-dose melphalan, 2: cyclophosphamide and total body irradiation ± antithymocyte globulin and 3: idarubicin, busulfan and cyclophosphamide and idarubicin, cyclophosphamide and total body irradiation. Horizontal reference lines correspond to citrulline = 10 μM (solid), citrulline = 20 μM (dotted). Horizontal axis: day after start conditioning.

same is true for children (citrulline cut-off, 19 μM) [24]. Circulating citrulline concentrations can also help evaluate the graft rejection 3 months after intestinal transplant, the sensitivity for the detection moderate or severe acute rejection was high (sensitivity of 96%, specificity 68.6%, negative predictive value >99%) when a <13 μM was adopted as a cut-off [16].

Thus, an assessment score on the basis of citrulline is objective, validated at least by analogy, reproducible, reliable, specific and sensitive and meets the criteria proposed by MASCC and ISOO [4] better than any other scoring system to measure intestinal mucositis.

Moreover, an assessment score can be on the basis of either the level of citrulline or the AUC. Both are able to discriminate between different regimens which is important for research and practical purposes.

The area under the 10/citrulline is probably only appropriate for research purposes since the myeloablative regimen is the main determinant of the course of intestinal mucositis [21], and only a few measurements will be necessary to estimate the AUC. This version resembles the oral mucositis assessment scale (OMAS) designed as a research tool for determining and following the progress of OM [25]. The OMAS measures a consensus of indicators of OM severity and both the mean mucositis score and the extent of severe mucositis score, calculated over time either as the AUC or as the average of the three highest values, produce scores that are reproducible and responsive to change.

For clinical purposes, a scoring system on the basis of absolute citrulline values seems practical for determining intestinal mucosal barrier damage. The level of citrulline following myeloablative chemotherapy may help select those patients who will benefit from parenteral nutrition as is the case for those with villous atrophy, where a citrulline level <10 μM is highly predictive for the need of parenteral nutrition whereas a level >10 μM will allow weaning off of parenteral nutrition [11, 18]. Furthermore, we have shown low citrulline concentrations to be associated with bacteraemia [26], which could indicate that extra measures should be taken, for example, more intensive monitoring of vital signs and temperature registration. The duration of citrullinaemia below a certain threshold might also prove useful for grading the severity of gut mucositis as is now the case with grade 4 neutropenia of <7–10 days for which the course of antibiotic therapy is shorter than for those with a more protracted duration [27]. For intestinal mucositis, it is conceivable that parenteral nutrition should only be given to patients receiving regimens that induce a long duration of a citrullinaemia <10 μM since parenteral nutrition can promote villous atrophy, increase intestinal permeability and enhance bacterial translocation. Furthermore, knowledge of the expected duration of citrullinaemia <10 μM may help clarify when cytoprotective drugs are necessary and also when antimicrobial therapy should be initiated.

An assessment score on the basis of circulating citrulline concentrations offers a promising approach to studying the

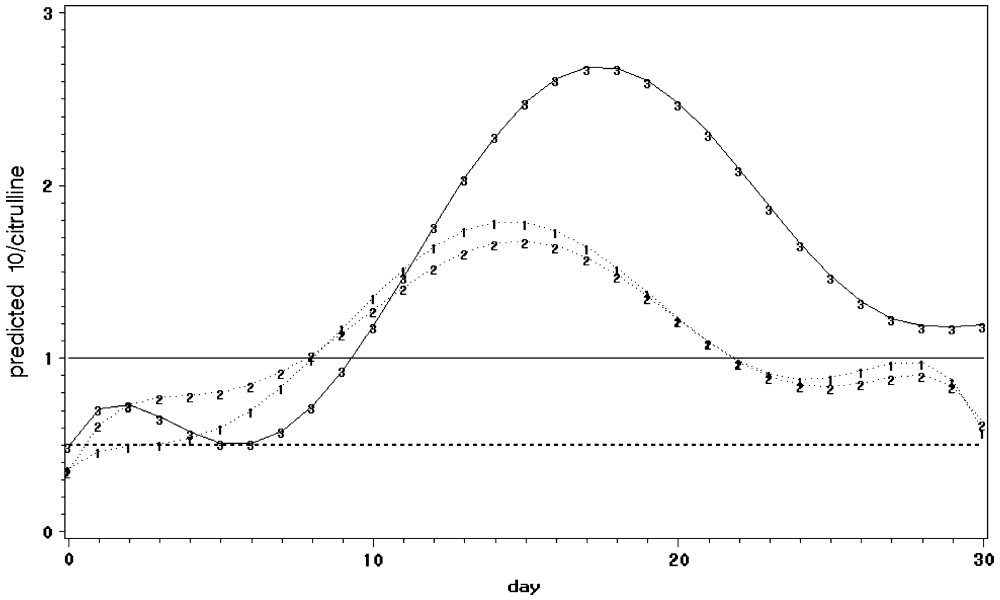

Figure 2. Course of citrulline over 30 days from start of the conditioning regimen depicted by average predicted values of 10/citrulline. On the basis of the area under the curve, the most severe intestinal mucositis was seen in group 3, consisting of the idarubicin-containing regimens. The mean area under the modelled 10/citrulline curves of group 3 was 44.7 day/μM, compared with 32.8 day/μM in group 1 and 32.6 day/μM in group 2. Vertical axis: predicted values of 10/citrulline in 10/μM. Numbers refer to the groups are 1: carmustine, etoposide, cytarabine and melphalan and high-dose melphalan, 2: cyclophosphamide and total body irradiation ± antithymocyte globulin and 3: idarubicin, busulfan and cyclophosphamide and idarubicin, cyclophosphamide and total body irradiation. Horizontal reference lines correspond to citrulline = 10 μM (solid), citrulline = 20 μM (dotted). Horizontal axis: day after start conditioning.

relationship between intestinal mucositis and post-transplant complications in general including GVHD. Further studies are necessary to explore the predictive value of citrulline for individual patients and to define suitable cut-off values. It is likely, that a citrulline-based assessment score could also be of help in the development of successful preventive interventions of agents such as interleukin 11 and keratinocyte growth factor that ameliorate alimentary tract mucositis [28, 29]. Patients treated with non-myeloablative regimens, those being treated for solid tumours or with radiotherapy may also benefit from the availability of a better tool for measuring intestinal mucositis.

In conclusion, circulating citrulline concentrations are able to discriminate between the extent and duration of intestinal mucosal damage induced by different high-dose chemotherapy regimens in the clinical setting. A citrulline-based assessment score should be considered the first choice for measuring and monitoring intestinal damage following myeloablative chemotherapy.

acknowledgements

Authors' contributions: AHH and NMB conceived the study. AHH and NMB wrote and reviewed the manuscript. JPD helped to draft the manuscript. TF carried out the statistical analysis. All authors have full access to all the data in the study, have read and approved this version of the article and agree with final submission. No part of this paper has published or submitted elsewhere. The authors have no funding to report.

disclosure

None of the authors declares a conflict of interest.

references

1. Rapaport AP, Miller Watelet LF, Linder T et al. Analysis of factors that correlate with mucositis in recipients of autologous and allogeneic stem-cell transplants. J Clin Oncol 1999; 17: 2446–2453.
2. Sonis ST, Oster G, Fuchs H et al. Oral mucositis and the clinical and economic outcomes of haematopoetic stem-cell transplantation. J Clin Oncol 2001; 19: 2201–2205.
3. Elting LS, Cooksley C, Chambers M et al. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 2003; 98: 1531–1539.
4. 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.
5. National Cancer Institute. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Bethesda, MD: National Cancer Institute. 2006.
6. World Health Organization. Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland: WHO Offset Publication No. 48. 1997.
7. Quinn B, Potting CM, Stone R et al. Guidelines for the assessment of oral mucositis in adult chemotherapy, radiotherapy and haematopoietic stem cell transplant patients. Eur J Cancer 2008; 44(1): 61–72.
8. Fallows G, Rubinger M, Bernstein CN. Does gastroenterology consultation change management of patients receiving hematopoietic stem cell transplantation. Bone Marrow Transplant 2001; 28: 289–294.
9. Blijlevens NMA, Donnelly JP, Pauw BE. Prospective evaluation of gut mucosal barrier injury following various myeloablative regimens for haematopoietic stem cell transplant. Bone Marrow Transplant 2005; 35: 707–711.
10. Keefe DM. Intestinal mucositis: mechanisms and management. Curr Opin Oncol 2007; 19(4): 323–327.

11. Crenn P, Vahedi K, Lavergne-Slove A et al. Plasma citrulline: a marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology 2003; 124: 1210–1219.
12. Blijlevens NMA, Lutgens LCHW, Schattenberg AVMB, Donnelly JP. Citrulline: a potentially simple quantitative marker of intestinal epithelial damage following myeloablative therapy. Bone Marrow Transplant 2004; 34(3): 193–196.
13. Lutgens LC, Deutz NE, Geuelette J et al. Citrulline: a physiologic marker enabling quantification and monitoring of epithelial radiation-induced small bowel damage. Int J Radiat Oncol Biol Phys 2003; 57(4): 1067–1074.
14. Crenn P, De Truchis P, Neveux N et al. Plama citrulline is a biomarker of enterocyte mass and an indicator of parenteral nutrition in HIV-infected patients. Am J Clin Nutr 2009; 90: 587–594.
15. Crenn P, Coudray-Lucas C, Thuillier F et al. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology 2000; 119(6): 1496–1505.
16. David AI, Selvaggi G, Ruiz P et al. Blood citrulline level is an exclusionary marker for significant acute rejection after intestinal transplantation. Transplantation 2007; 84(9): 1077–1081.
17. Keefe D, Brealey J, Goland G, Cummins A. Chemotherapy for cancer causes apoptosis that precedes hypoplasia in crypts of the small intestine in humans. Gut 2000; 47(5): 632–637.
18. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clin Nutr 2008; 27(3): 328–339.
19. Ceballos I, Chauveau P, Guerin V et al. Early alterations of plasma free amino acids in chronic renal failure. Clin Chim Acta 1990; 188: 101–108.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.
21. Wardley AM, Jayson GC, Swindell R et al. Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haematopoietic progenitor rescue. Br J Haematol 2000; 110: 292–299.
22. Van Eijk HM, Rooyakkers DR, Deutz NE. Rapid routine determination of amino acids in plasma by high-performance liquid chromatography with a 2–3 microns Spherisorb ODS II column. J Chromatogr 1993; 620: 143–148.
23. Lutgens LC, Blijlevens NM, Deutz NE et al. Monitoring myeloablative therapy-induced small bowel toxicity by serum citrulline concentration: a comparison with sugar permeability tests. Cancer 2005; 103: 191–199.
24. Rhoads JM, Plunkett E, Galanko J et al. Serum citrulline levels correlate with enteral tolerance and bowel length in infants with short bowel syndrome. J Pediatr 2005; 146(4): 542–547.
25. Sonis ST, Eilers JP, Epstein JB et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiotherapy or chemotherapy. Cancer 1999; 85(10): 2103–2113.
26. Herbers AH, Blijlevens NM, Donnelly JP, de Witte TJ. Bacteraemia coincides with low citrulline concentrations after high-dose melphalan in autologous HSCT recipients. Bone Marrow Transplant 2008; 42(5): 345–349.
27. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia. Risks, consequences and new directions for its management. Cancer 2004; 100: 228–237.
28. Ellis M, Zwaan F, Hedstrom U et al. Recombinant human interleukin 11 and bacterial infection in patients with haematological malignant disease undergoing chemotherapy: a double-blind placebo-controlled randomised trial. Lancet 2003; 25: 275–280.
29. Spielberger R, Stiff P, Bensinger W et al. Palifermin for oral mucositis after intensive therapy for hematologic cancer. N Engl J Med 2004; 351: 2590–2598.