available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Parenteral nutrition is not superior to replacement fluid therapy for the supportive treatment of chemotherapy induced oral mucositis in children

Irene Schmid[a,*], *Melanie Schmitt*[a], *Monika Streiter*[a], *Rita Meilbeck*[a], *Michael H. Albert*[a], *Dietrich Reinhardt*[a], *Daniel Stachel*[b]

[a]*Kinderklinik and Kinderpoliklinik, Dr. von Haunersches Kinderspital, Ludwig-Maximilians-University Munich, Lindwurmstr. 4, D-80337, Munich, Germany*

[b]*Department of Paediatrics, Paediatric Hematology and Oncology, University of Erlangen-Nurnberg, Erlangen, Germany*

ARTICLE INFO

Article history:
Received 18 July 2005
Received in revised form
19 August 2005
Accepted 27 September 2005
Available online 5 December 2005

Keywords:
Mucositis
Children
Cancer
Parenteral nutrition
Replacement fluid therapy
Nutritional status

ABSTRACT

Many paediatric oncology centres apply parenteral nutrition (PN) in children with severe oral mucositis after chemotherapy. However, no convincing data exist to support this treatment strategy. The aim of our study was to elucidate a possible advantage of PN versus intravenous replacement fluid therapy (FT). In a prospective randomized study, 30 children with mucositis WHO grade IV were assigned to receive either PN or intravenous replacement FT. Weight, total body water, fat-free mass (measured by impedance analysis) and peripheral white blood cells were assessed daily. For aspects of quality of life and economics, the length of hospital stay, the incidence of infections, the days on intravenous antibiotics and delay of scheduled chemotherapy were examined. Children with PN gained body weight significantly compared to baseline and to FT due to an augmentation of fat mass while total body water and fat-free mass significantly decreased. In children with FT, body weight remained stable while total body water and fat-free mass significantly increased, thereby loosing fat mass. We observed no differences in recovery of peripheral white blood cells (WBC), incidence of infections, hospitalization time, days on intravenous antibiotics, days on opioid analgesics and delay of the next scheduled chemotherapy cycle. Although children with PN gained weight in form of fat mass, this did not translate into a clinical benefit for the patients such as earlier recovery of WBC counts, shorter hospitalization time, a decreased use of analgesics or less delay of the next scheduled chemotherapy cycle. Our findings therefore do not support the hypothesis that PN is superior to FT when used for less than 10 days for oral mucositis.

1. Introduction

Oral mucositis is one of the most debilitating side-effects of intensive chemotherapy. Approximately, 50% of children receiving chemotherapy for malignancies develop at least one complication confined to the oral cavity [1,2]. The mechanisms leading to the development of mucositis involve a complex combination of a direct effect of cytotoxic drugs on the basal epithelium and connective tissue, the oral microbial environment and local release of inflammatory cytokines

* *Corresponding author*: Tel.: +49 89 5160 2842; fax: +49 89 5160 4719.
E-mail address: Irene.Schmid@med.uni-muenchen.de (I. Schmid).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.09.020

[3–5]. Oral mucositis begins shortly after therapy and peaks in severity around day 7–10 of therapy with resolution occurring within 2 weeks [2,6]. The lesions can result in severe morbidity with pain as the hallmark symptom necessitating the use of analgesics. Other frequent complications include decreased or completely abolished oral intake leading to weight loss and malnutrition, an increased risk of systemic infection due to disrupted mucosal barrier and extended hospitalization time [2,4]. All these conditions substantially decrease the quality of life and may jeopardize survival especially when chemotherapy treatment needs to be delayed or modified.

Although oral mucositis has been studied for many years, no available treatment has proven to be reliably effective to prevent or treat mucositis [7]. Studies investigating single antimicrobial agents such as chlorhexidine [8], clindamycin [9], or antibiotic pastilles combining polymyxin, tobramycin and amphotericin [10] given locally with the intent of enhancing oral hygiene have shown only variable success alleviating oral mucositis. Only very recently, keratinocyte growth factor (KGF, palifermin) has demonstrated a clear benefit in adults with severe chemotherapy induced mucositis, while none of the other growth factors and cytokines like GM-CSF have a clear beneficial impact on mucositis [11–15].

In many centres, parenteral nutrition (PN) is started as soon as oral mucositis develops to prevent patients from entering a catabolic metabolic state. However, there are no published data showing a convincing benefit of PN. On the other hand it has been shown that the infection rate is significantly increased in patients receiving PN [16,17]. This is least desirable in patients already prone to infections due to neutropenia. In this study, we have conducted a prospective randomized trial in children with cancer treated with multiagent chemotherapy to examine if parenteral nutrition improves the outcome of mucositis compared to mere fluid replacement therapy (FT). Endpoints were nutritional status, recovery of white blood cells, use of intravenous analgesics, incidence of infection, hospitalization time and delay of scheduled chemotherapy.

2. Patients and methods

2.1. Patients

After informed consent by their care-givers 30 children (1–18 years) receiving first-line intensive standard-dose chemotherapy for malignancies were prospectively investigated. Intensive standard-dose chemotherapy was defined as multiagent chemotherapy cycles during consolidation therapy in haematological patients or in patients with solid tumours according to national or international standard treatment protocols for paediatric cancer. Starting on the day that oral mucositis WHO grade IV developed and intravenous (i.v.) opioid analgesics were initiated, they were randomized to receive either PN or FT. Patient characteristics are presented in Table 1. WHO Grade IV mucositis was defined as painful ulceration, erythema or edema and with inability to swallow [4]. Five children were recruited twice, two were randomized in both arms, one twice in the PN group and two twice in the FT group. There was no influence of the first episode on the second episode (data not shown). Nasogastric tube feeding was not used because of already existing chemotherapy-induced mucosal damage. The study was designed to exclusively address the question whether PN was superior to FT without additional enteral feeding. Exclusion criterions were parental refusal to participate in the study and the use of intravenous analgesics for less than 5 days.

Table 1 – Patient characteristics

	PN (n = 15)	FT (n = 15)
Age (years)	8.2 (2.0–15.2)	8.1 (2.1–17.2)
Male/female	7/8	11/4
Type of cancer		
ALL	7	5
MDS	1	1
NHL	4	5
Hodgkin's disease	0	2
Hepatocellular carcinoma	0	1
Osteosarcoma/undifferentiated sarcoma	1	1
PNET	1	0
Nasopharyngal carcinoma	1	0

PN, parenteral nutrition; FT, fluid replacement therapy.

2.2. Definition of therapies

Patients randomized to FT received intravenous fluids and electrolytes according to the baseline recommendations of the German Society for Nutrition [19]. In brief, children between 1 and <4 years received 95 ml/kg/d; 4 and <7 years 75 ml/kg/d; 7 and <10 years 60 ml/kg/d; 10 and <13 years 50 ml/kg/d; and 13 and <19 years 40 ml/kg/d. The intravenous fluid consisted of NaCl 0.45% and glucose 2.5% supplemented with electrolytes as necessary.

Patients randomized to parenteral nutrition received the same amount of intravenous fluid and electrolytes as the children on fluid replacement therapy with standard formulations of carbohydrates, lipids, amino acids, vitamins and trace elements given at doses recommended by the German Society for Nutrition [19] over 24 h. In brief, children between 1 and <4 years received 90 kcal/kg/d; 4 and <7 years 80 kcal/kg/d; 7 and <10 years 70 kcal/kg/d; 10 and <13 years 60 kcal/kg/d; 13 and <15 years 50 kcal/kg/d; and 15 and <19 years 45 kcal/kg/d. More than 50% of the total amount of calories was supplied as glucose. The daily fat supply was 1.5–2 g/kg/d (35–45% of total calories). The amino acid supply was 1.5–2.0 g/kg/d for children between 1 and <4 years; and 1.3–1.8 g/kg/d for children between 4 and <19 years.

2.3. Anthropometry

Weight was measured daily to the nearest of 0.1 kg using an electronic scale (SECA, Vogel&Halke, Hamburg, Germany) and height (or supine length for children <2 years) once at admission to the nearest of 0.1 cm using a stadiometer (System Dr. Keller I, Limbach-O, Germany).

Total body water, fat-free mass and the phase angle were determined daily by bioelectrical impedance analysis (BIA-

2000-M, Data-Input, Frankfurt, Germany, Nutri 4). Fat-free mass was calculated by using the equation of Goran [18]. Total body water and fat-free mass were expressed as percentage of body weight. The phase angle is the arctan of resistance to reactance and is directly proportional to body cell mass. Reduced phase angles are consistent with either cell death or a breakdown in the selective permeability of the cell membrane [20].

2.4. *Laboratory parameters*

White blood cells, blood urea nitrogen, creatinine, albumin and prealbumin were determined by standard methods on automated clinical chemistry analyzers. In brief, white blood cells were determined on a Coulter Micro Diff II (Beckman Coulter GmbH Biomedical Research, Krefeld, Germany); urea nitrogen, creatinine and albumin on a Hitachi 912 Automatic Analyzer (Roche Diagnostics, Basel, Suisse); and prealbumin on an Array (Beckman Coulter GmbH Biomedical Research, Krefeld, Germany) with reagents from the same supplier. WBC recovery was defined as the time until white bloods cells exceeded 1000/μl of whole blood.

2.5. *Prophylactic measures and definition of infection*

All children cleaned the oral cavity with a solution containing chlorhexidine at least four times a day. Aciclovir was given intravenously to all children who were seropositive for herpes simplex virus (HSV).

An infection was diagnosed as soon as a blood, stool or urine culture turned out to be positive for bacteria, virus or fungus. Empiric intravenous antibiotics (ceftazidim and tobramycin) were started whenever fever occurred (defined as body temperature exceeding 38.5 °C) and extended in the case of non-defervescence according to standard hospital operating procedures. The days on i.v. antibiotics was evaluated by counting each antibiotic agent every day for the whole episode of mucositis for each patient. Prophylactic granulocyte colony stimulating factor (G-CSF) was given in five patients in the PN group and four patients in the fluid replacement group.

2.6. *Statistical analysis*

Data are expressed as median values. Statistical significance comparing both groups was done using the Mann–Whitney–Wilcoxon test. For comparing time variables at days 1 and 10, Kaplan–Meier life table analyses were used. A log-rank test was used to compare the time variables between both groups. Differences were considered significant at $P < 0.05$. The SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

3.1. *Body composition studies*

To assess whether the application of PN is able to positively influence the body composition of patients compared to FT alone, we utilized body weight and bioelectrical impedance analysis to measure total body water, fat-free mass and body cell mass.

In the PN group, body weight (Fig. 1(a)) increased during the course of therapy ($P < 0.001$, day 10 versus day 1), whereas it remained stable in the group with FT ($P = 0.321$). We also observed a significant difference between the PN and the FT group starting at day 4 ($P < 0.005$) until the end of the study period. The total body water (Fig. 1(b)) decreased in the PN group ($P = 0.006$, day 1 versus day 10), whereas it increased in the FT group ($P = 0.034$) during the course of the disease. There was no significant difference between both groups. The fat-free mass (Fig. 1(c)) decreased in the PN group ($P = 0.02$) and increased in the FT group ($P = 0.03$), however, with no significant difference between both groups. The phase angle (Fig. 1(d)) and thus the body cell mass remained stable in the PN group ($P = 0.51$ day 1 versus day 10) and decreased slightly in the FT group ($P = 0.09$). There was no difference between both groups in the course of the disease. These data indicate that PN has no positive effect on body composition but significantly increased body weight.

3.2. *Laboratory parameters*

We hypothesized that PN leads to a faster recovery of WBC counts, since PN has been reported to accelerate recovery of normal bone marrow [24,25]. To further find out whether the kind of therapies influenced laboratory parameters, an indication of the metabolic state, we investigated urea nitrogen, creatinine, albumin and prealbumin levels in serum during the course of therapy. Contrary to our hypothesis, the duration until recovery of WBC counts was not different between the PN group and the FT group ($P = 0.865$) (Fig. 2). The median time to recovery was 4 days in both groups. Administration of G-CSF did not differ between the groups. Levels of urea nitrogen, creatinine, albumin and prealbumin remained unchanged compared to baseline during the study time in both groups and were also not significantly different between the groups (data not shown).

These data showed no improvement in recovery of WBC counts in patients receiving PN compared to FT. In addition indicators of metabolic state such as urea nitrogen, creatinine, albumin and prealbumin remained stable and were not influenced by the regimen used.

3.3. *Clinical parameters*

With no significant advantage in WBC recovery for the PN group, we next asked whether this treatment led to any clinical benefit for patients. For aspects of quality of life, hospitalization time due to mucositis, delay of scheduled chemotherapy, days on opioid analgesics, the incidence of infections and days on intravenous antibiotics were examined. Patients with PN had a median hospitalization time of 14 days as compared to 13 days for children with FT (Fig. 3(a)) ($P = 0.817$). Regularly scheduled chemotherapy following the cycle that induced the mucositis according to the respective treatment protocol had to be delayed for a median of 6 days in the PN group and 5 days in the FT group (Fig. 3(b)) which was not statistically different ($P = 0.627$). Intravenous opioid analgesics were necessary for a median of 5 days in the group with PN and 6 days in the group with FT (Fig. 3(c)) ($P = 0.345$). Culture positive infections were

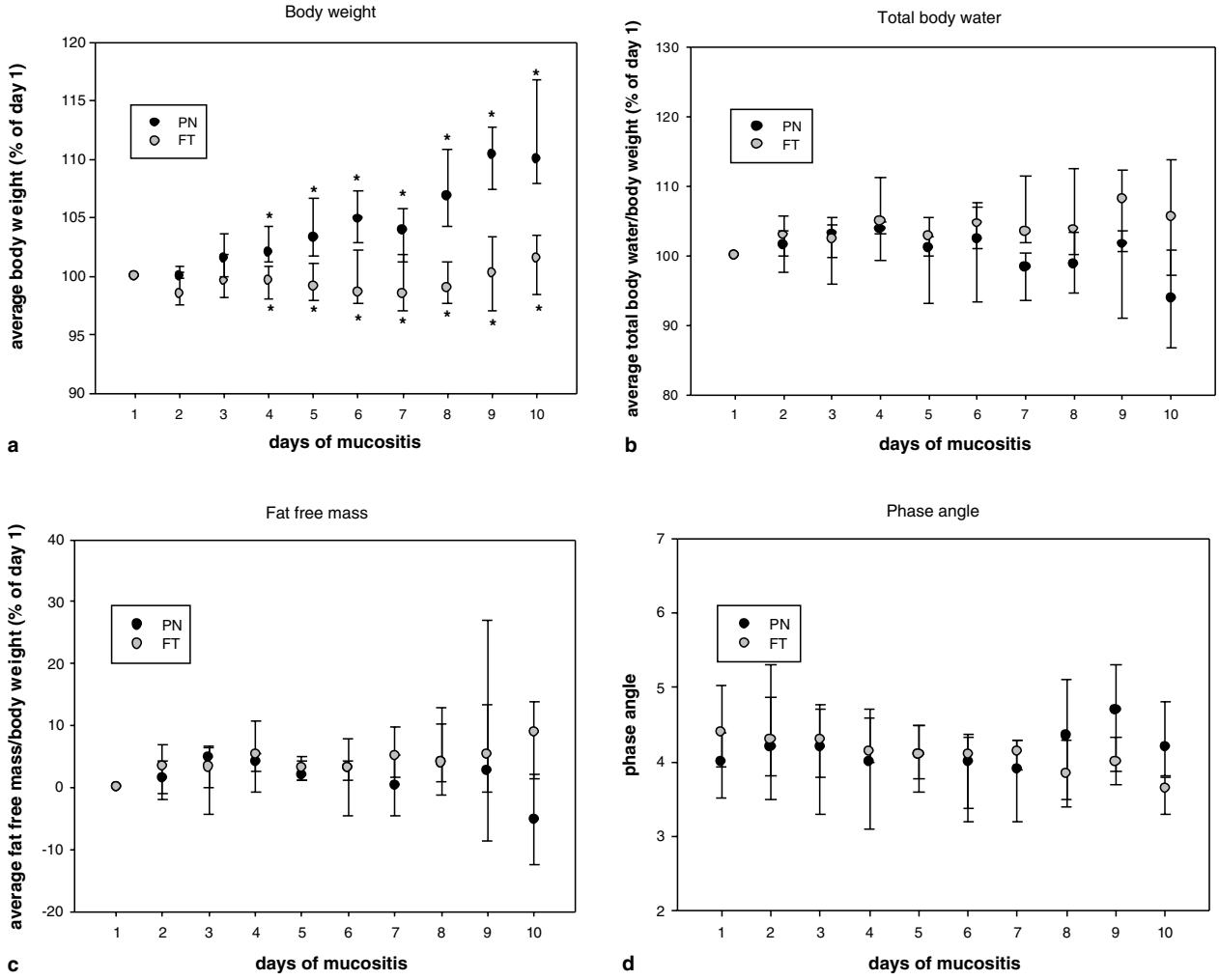

Fig. 1 – Body composition studies. (a) Development of body weight; (b) total body water; (c) fat-free mass; (d) and phase angle during the study period in the group receiving PN (full symbols) and FT (empty symbols). * delineates statistically significant differences between the two groups ($P < 0.05$). Data are presented as median and 25th and 75th percentile (whiskers).

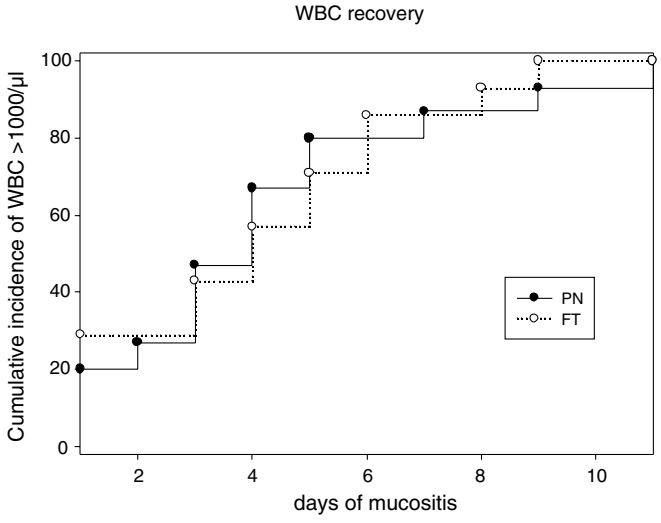

Fig. 2 – WBC recovery. Cumulative incidence of patients reaching over 1000/µl WBC during the study period. Graph curves do not start at 0% and do not end at 100% because of patients never dropping below or not reaching 1000/µl WBC during the study period, respectively.

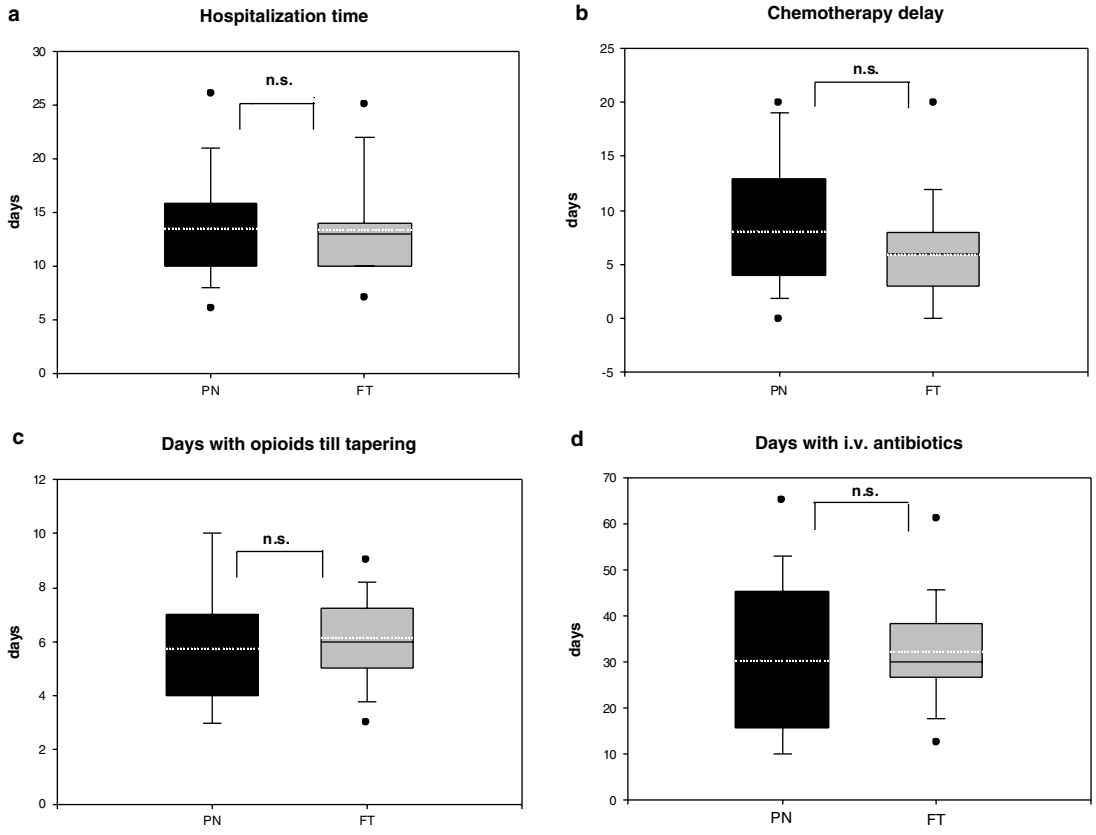

Fig. 3 – Clinical parameters. (a) Duration of hospitalization due to mucositis in days; (b) delay of scheduled chemotherapy; (c) length of opioid analgetic use; (d) and days on i.v. antibiotics in the PN (black boxes) and FT group (gray boxes), respectively. Data are presented as median (solid line), mean (dotted line), 25th and 75th percentile (boxes), 10th and 90th percentile (whiskers) and outliers (solid dots).

Table 2 – Patient infections during course of treatment

	PN (n = 15)	FT (n = 15)	
Culture positive infections (%)	8 (53)	4 (27)	P = 0.136
Infectious agents (more than one infectious agent identified in some patients)	Bacteremia (2) Invasive mycosis (1) Oropharyngeal candidiasis (2) Clostridium difficile enteritis (2) Viral enteritis (2)	Bacteremia (2) Oropharyngeal candidiasis (1) Urinary tract infection (1) Clostridium difficile enteritis (1) Viral enteritis (1)	

diagnosed in 8 of 15 children with PN (53%) in comparison to 4 in 15 children with FT (27%, P = 0.136, Table 2). The PN group had a median of 2 days with fever (not shown) and 34 days on intravenous antibiotics as compared to 3 and 33 days, respectively, in the FT group (Fig. 3(d)) (P = 0.53). Thus, it appears that PN does not lead to clinical benefits for the patient such as shorter hospitalization time, less delay of chemotherapy, decreased need for opioids or less infections and antibiotic use.

4. Discussion

In many centres costly PN is frequently used in the belief that this approach may improve the clinical course of mucositis. Reliable data supporting this approach, however, are not available. For the first time, we have clearly demonstrated in a prospective randomized study that PN is not superior to FT in treating children with cancer suffering from severe mucositis.

We have found that PN did not reduce hospitalization time, days on intravenous antibiotics and the delay of the next scheduled chemotherapy cycle and thus quality of life. Although children with PN significantly gained body weight, body composition studies revealed that this increase is due to an augmentation of fat mass (and not lean body mass). In children with mere parenteral FT, body weight remained stable, while total body water and fat-free mass significantly increased. Thus patients loose fat mass when they receive fluid therapy during chemotherapy induced mucositis. Similar disappointing results have been shown in adult patients

during chemotherapy courses. In these patients, PN did not improve the accrual of lean body mass, did not improve nutritional parameters nor did it ameliorate treatment toxicity [21,22]. The results of a meta-analysis of prospective randomized trials in adults suggest that waiting 7–10 days to initiate any form of aggressive nutrition intervention may be prudent for normally nourished populations with compromised gastrointestinal function [23]. Consequently, it is the policy of the St. Jude Children's Research Hospital in Memphis not to start nutritional therapy if the time of the inability of oral intake is expected to be less than 7 days [24]. Our study results strongly support this strategy since parenteral nutrition did not induce a clinical benefit in our paediatric patients. As an alternative, enteral feeding via nasogastric tube (or gastrostomy) placed before the onset of mucositis is a standard of clinical practice in many centres. A limited number of studies have been published comparing enteral nutrition with PN, however, almost exclusively in stem-cell transplant recipients [25]. One study in children receiving intensive chemotherapy showed a significant cost advantage of enteral tube feeding [26]. Further prospective studies should be undertaken to address this issue.

Advocates of parenteral nutrition use have argued that host defense against infection may be improved by parenteral nutrition through accelerated recovery of normal marrow and through the promotion of mucosal repair after chemotherapy-induced mucositis [27,28]. The WBC counts in this study did not recover faster with parenteral nutrition. However, there was a trend towards a higher incidence of infections in the group with parenteral nutrition. This is in accordance with a meta-analysis, where parenteral nutrition was significantly associated with more infections [16,17]. Indeed, results of studies using parenteral nutrition to improve recovery from severe myelosuppression and tolerance towards more intensive treatment have been inconsistent. Randomized prospective studies show a benefit of parenteral nutrition compared to an oral ad libitum diet in children with metastatic disease and acute non-lymphoblastic leukaemia [17,29,30]. Parenteral nutrition was superior to peripheral nutrition plus enteral nutrition in reversing protein energy malnutrition and prevented delays in chemotherapy and radiotherapy due to granulocytopenia in 13 children with nephroblastoma at high risk for malnutrition [31]. In contrast, other studies failed to document a benefit in accelerating recovery from severe myelosuppression in patients with poor prognosis sarcoma (median age 17 years) [32] or lymphoma [33]. Cetin and colleagues [34] even reported a delayed recovery of platelets and a higher need for platelet transfusions after blood stem-cell transplantation in patients receiving PN.

In conclusion, our randomized study showed an increase of body weight in form of fat mass as the only effect of PN during chemotherapy induced mucositis in children. However, this did not lead to a faster recovery of WBC count, shorter hospitalization time, shorter need of antibiotics or less delay of the next chemotherapy cycle. In addition, the infection rate was not significantly different in the PN and FT group. Therefore, from a clinical and an economic viewpoint, our study results do not support the initiation of short-term parenteral nutrition during the course of oral mucositis in children.

Conflict of interest statement

None declared.

Acknowledgements

This work was supported by the Bettina-Bräu-Stiftung, the Christina-Bergmann-Stiftung and the Friedrich-Baur-Stiftung.

REFERENCES

1. Bonnaure-Mallot M, Bunetel L, Tricot-Doleux S, et al. Oral complications during treatment of malignant diseases in childhood: effects of tooth brushing. *Eur J Cancer* 1998;**34**:1588–91.
2. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy: clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* 2003;**98**:1531–9.
3. Sonis ST. Mucositis as a biological progress: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol* 1998;**34**:39–43.
4. Wilkes JD. Prevention and treatment of oral mucositis following cancer chemotherapy. *Semin Oncol* 1998;**25**:538–51.
5. 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**(Suppl. 9):1995–2025.
6. Sonis ST, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. *Oncology* 1991;**5**:11–8.
7. Rubenstein EB, Peterson DE, Schubert M, et al. for the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004;**100**(Suppl. 9):2026–46.
8. Cheng KKF, Chang AM, Yuen MP. Prevention of oral mucositis in paediatric patients treated with chemotherapy: a randomised crossover trial comparing two protocols of oral care. *Eur J Cancer* 2004;**40**:1208–16.
9. Donnelly JP, Muus P, Horrevorts AM, et al. Failure of clindamycin to influence the course of severe oromucositis associated with streptococcal bacteriaemia in allogeneic bone marrow transplantat recipients. *Oral Surg Oral Med Oral Pathol* 1992;**73**:682–9.
10. Symonds RP, Mellroy P, Khorrami J, et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. *Br J Cancer* 1996;**74**:312–7.
11. Chi KH, Chen CH, Chan WK, et al. Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil, and leucovorin. *J Clin Oncol* 1995;**13**:2620–8.
12. Dazzi C, Cariello A, Giovanis P, et al. Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumours undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double blind, randomized, placebo-controlled study. *Ann Oncol* 2003;**14**:559–63.

13. Karthaus M, Rosenthal C, Ganser A. Prophylaxis and treatment of chemo- and radiotherapy-induced mucositis – are there new strategies? *Bone Marrow Transplant* 1999;**24**:1095–108.
14. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *New Engl J Med* 2004;**351**:2590–8.
15. Foncuberta MC, Cagnoni PJ, Brandts CH, et al. Topical transforming growth factor-ß3 in the prevention or alleviation of chemotherapy-induced oral mucositis in patients with lymphomas or solid tumours. *J Immunother* 2001;**24**:384–8.
16. Christensen ML, Hancock M, Gattuso J, et al. Parenteral nutrition associated with increased infection rate in children with cancer. *Cancer* 1993;**72**:2732–8.
17. Ghavimi F, Shils ME, Scott BF, et al. Comparison of morbidity in children requiring abdominal radiation and chemotherapy, with and without total parenteral nutrition. *J Pediatr* 1982;**101**:530–7.
18. Goran MI, Kaskoun MC, Carpenter WH, et al. Estimating body composition of young children by using biolelectrical resistance. *J Appl Physiol* 1993;**75**:1776–80.
19. Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährungsforschung, Schweizerische Vereinigung für Ernährung (D-A-CH). Referenzwerte für die Nährstoffzufuhr. 1. Auflage, Frankfurt: Umschau Braus GmbH, 2000.
20. Baumgartner RN, Chumlea WC, Roche AF. Bioelectrical impedance phase angle and body composition. *Am J Clin Nutr* 1988;**48**:16–23.
21. Harrison LE, Brennan MF. The role of parenteral nutrition in the patient with cancer. *Curr Probl Surg* 1995;**32**:835–917.
22. Popp MB, Fischer RI, Wesley R. A prospective randomized study on adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: influence on survival. *Surgery* 1981;**90**:195–203.
23. Braunschweig CL, Levy P, Sheean PM, et al. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr* 2001;**74**:534–42.
24. Bowman LC, Williams R, Sanders M, et al. Algorithm for nutritional support: experience of the Metabolic and Infusion Support Service of St. Jude Children's Research Hospital. *Int J Cancer Suppl* 1998;**11**:76–80.
25. Murray SM, Pindoria S. Nutrition support for bone marrow transplant patients. *Cochrane Database Syst Rev* 2002, CD002920.
26. Pietsch JB, Ford C, Whitlock JA. Nasogastric tube feedings in children with high-risk cancer: a pilot study. *J Pediatr Hematol Oncol* 1999;**21**:111–4.
27. Taj MM, Pearson AD, Mumford DB, et al. Effect of nutritional status on the incidence of infection in childhood cancer. *Pediatr Hematol Oncol* 1993;**10**:283–7.
28. Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double-blind, controlled study. *Ann Intern Med* 1992;**116**:821–8.
29. Hays DM, Merritt RJ, White L, et al. Effect of total parenteral nutrition on marrow recovery during induction therapy for acute nonlymphocytic leukemia in childhood. *Med Pediatr Oncol* 1983;**11**:134–40.
30. Van Eys J, Copeland EM, Cangir A, et al. A clinical trial of hyperalimentation in children with metastatic malignancies. *Med Pediatr Oncol* 1980;**8**:68–73.
31. Rickard KA, Godshall BJ, Loghmani ES, et al. Integration of nutrition support into oncologic treatment protocols for high and low nutritional risk children with Wilms tumour. A prospective randomized study. *Cancer* 1983;**64**:491–509.
32. Shamberger RC, Pizzo PA, Goodgame JT, et al. The effect of total parenteral nutrition on chemotherapy-induced myelosuppression. A randomized study. *Am J Med* 1983;**74**:40–8.
33. Popp MB, Fisher RI, Simon RM, et al. A prospective randomized study of adjuvant parenteral nutrition in the treatment of diffuse lymphoma: effect on drug tolerance. *Cancer Treat Rep* 1981;**65**(Suppl. 5):129–35.
34. Cetin T, Arpaci F, Dere Y, et al. Total parenteral nutrition delays platelet engraftment in patients who undergo autologous hematopoietic stem cell transplantation. *Nutrition* 2002;**18**:599–603.