Original article

Prevention of mucositis in bone marrow transplantation: A double blind randomised controlled trial of sucralfate

L. Castagna,[1,4] E. Benhamou,[2] E. Pedraza,[1] M. Luboinski,[2] M. Forni,[3] I. Brandes,[1] J.-L. Pico[1] & P.-Y. Dietrich[1,3]

[1]*Department of Haematology, BMT Unit,* [2]*Biostatistics, Institut Gustave Roussy, Villejuif, France;* [3]*Division of Oncology, University Hospital, Geneva, Switzerland;* [4]*Present address: Oncology-Hematology Department, Istituto Clinico Humanitas, Rozzano (MI), Italy*

Summary

Mucositis is still a leading side effect of high dose chemotherapy and irradiation delivered in autologous and allogeneic bone marrow transplantation. In this double blind randomised study, we tested the efficacy of sucralfate for the prevention of mucositis induced by such conditioning treatments. Treatment was started one day before conditioning regimen and patients were prospectively evaluated. The main endpoint was severe mucositis that was more frequent in the placebo group than in the sucralfate group (47% vs. 29%, $P = 0.07$). This trend was confirmed after adjustment on total body irradiation (TBI) ($P = 0.06$), the sole stratification parameter. Interestingly, patients receiving sucralfate showed a significant reduction of diarrhoea (25% vs. 53%, $P = 0.005$). Overall, the preventive administration of sucralfate appears to be an effective procedure to diminish the occurrence of severe oral and intestinal mucositis in patients treated by high dose chemotherapy alone or combined with TBI before bone marrow transplantation.

Key words: mucositis, stem-cell transplantation, sucralfate

Introduction

Mucositis is a dose-limiting toxicity that frequently complicates the course of autologous or allogeneic bone marrow transplantations (BMT) [1]. Efforts should focus on its prevention, since treatment of established lesions remains unsuccessful. Efficient prevention of toxic damage induced by conditioning regimens on intestinal mucosa will not only protect the patient from major pain, abdominal discomfort and diarrhoea, but could also improve food intake and reduce the risk of infections by diminishing the risk of microbial translocation from the digestive tract into the bloodstream [2].

Sucralfate is a complex salt of sucrose sulfate and aluminium hydroxide which is commonly used for the treatment of acute duodenal and gastric ulcer diseases. Its main mechanism of action is thought to be the adhesion of the drug to ulcerated mucosa, forming a physical barrier to protect them from acid, bile salts and pepsin. In addition, sucralfate has multiple biological effects, such as the induction of prostaglandin and mucus production, an increase in mucosal blood flow and the binding of epithelial growth factor and basic fibroblastic growth factor to tissues [3]. This suggested to us that this drug can be active in the prevention of mucositis. We report the results of a monocentric prospective randomised double blind study designed to evaluate the efficacy of sucralfate to prevent mucositis after BMT.

Patients and methods

Treatment

Patients fulfilling the enrolment criteria (patients > 15 years old, hospitalised for a allogeneic or autologous BMT, provision of a written informed consent) were randomly allocated to the sucralfate or the placebo group, a few days before the beginning of the conditioning regimen. Conditioning regimens were categorised in four groups, based on their probability to induce mucositis (very high risk, high risk, intermediate risk, low risk) (Table 1). Randomisation was stratified on Total Body Irradiation (TBI). Patients were instructed to ingest one dose package (2 g) of sucralfate or an identical-appearing placebo every three hours daily and once during the night in case of wakening, for a maximum of seven mouthwashes per 24 hours. Sucralfate or placebo were to be kept within the mouth for one minute before being swallowed. Patients were asked to avoid drinking and eating during the first hour after treatment ingestion. Treatment was initiated after initial oral evaluation, one day before conditioning regimen and continued until bone marrow recovery (ANC ≥ 0.5×10^6/l) or until the end of mucositis (in the case of persistent mucositis after bone marrow recovery).

Patient evaluation

Patients were examined twice weekly from the first day of conditioning regimen until bone marrow recovery or resolution of clinical signs of mucositis. The clinical examination was performed by two physicians only, and results were prospectively recorded. The oral status was scored according to a toxicity grading adapted from OMS criteria for grafted patients (Table 2). The primary objective was to compare the occurrence of severe stomatitis (grade 3–4). Secondary objectives were to define (i) the duration of mucositis, (ii) the rate and severity of diarrhoea, and (iii) the caloric intake achieved by oral nutrition.

Table 1. Patients' characteristics before inclusion in study.

	Sucralfate $n = 51$ (%)	Placebo $n = 51$ (%)	P-value
Sex			
Male	34	34	NS
Female	33	33	NS
Diagnosis			
AL	11 (22)	18 (35)	
CML	4 (8)	5 (10)	
NHL	15 (29)	10 (20)	NS
HD	9 (18)	4 (8)	
Germinal tumour	4 (8)	6 (12)	
Other	8 (16)	8 (16)	
Previous chemotherapy	50 (98)	50 (98)	
1 line	18	18	
2 lines	20	23	NS
3 lines	11	5	
4 lines	1	4	
Previous radiotherapy	14 (27)	12 (24)	NS
Previous mucositis	28 (57)	35 (69)	NS
Conditioning regimen			
Group 1	5	6	NS
Group 2	25	24	NS
Group 3	6	10	NS
Group 4	15	11	NS
Total body irradiation	30 (59)	30 (59)	NS
Single dose (10 Gy)	18 (60)	16 (53)	NS
Hyperfractionated (14 Gy)	10 (33)	10 (33)	NS
Other	2 (7)	4 (13)	NS

Abbreviations: AL - acute leukaemia; CML - chronic myelogenous leukaemia; NHL: non-Hodgkin lymphoma; HD - Hodgkin's disease, BMT - bone marrow transplantation; PBSC - peripheral blood stem cells; NS - not significant.

Groups of conditioning regimens: *Group 1 very high risk.* TEC: TBI (single dose TBI at 10 Gy or hyperfractioned TBI at 14 Gy) + cyclophosphamide (120 mg/kg) + etoposide (60 mg/kg); *Group 2 high risk* TBI + cyclophosphamide (120 mg/kg), TBI + melphalan (140 mg/m^2), TAM 12: TBI + cytarabine (12 g/m^2) + melphalan (120 mg/m^2), TLI (total lymphoid irradiation) + cyclophosphamide (120 mg/kg), *Group 3 intermediate risk:* BuCy: busulphan (16 mg/kg) + cyclophosphamide (120 mg/kg), PEC: cisplatine (200 mg/m^2) + cyclophosphamide (120 mg/kg) + etoposide (1800 mg/m^2), CARBOPEC: carboplatine (800, 1200, or 1600 mg/m^2) + cyclophosphamide (120 mg/kg) + etoposide (1800 mg/m^2), BusPAM: busulphan (16 mg/kg) + melphalan (140 mg/m^2), PAM: melphalan only (140 mg/m^2); *Group 4 low risk.* BEAM: BCNU (300 mg/m^2) + etoposide (400 mg/m^2) + cytarabine (400 mg/m^2) + melphalan (140 mg/m^2) BEAC: BCNU (300 mg/m^2) + etoposide (400 mg/m^2) + cytarabine (400 mg/m^2) + cyclophosphamide (120 mg/kg).

Table 2 Adapted toxicity grading for evaluation of oral mucosa.

Grade 0	No mucositis
Grade 1	Erythema or whitish mucosa
Grade 2	Superficial erosive lesions (< 20% of mucosa)
Grade 3	Extensive erosive lesions or ulcerations or painful swallowing
Grade 4	Impossibility to swallow and/or to protrude the tongue

Grade 0, 1, 2 were grouped as 'mild' and grade 3, 4 as 'severe'

Statistical methods

It was estimated that 100 patients should be included to demonstrate a minimal difference of 35% in the rate of severe mucositis (two tailed test, α = 5%, β = 5%). Analyses were carried out on the intention-to-treat principle. Differences between groups were evaluated by χ^2 test or Fisher's exact test for categorical variables and Student's t-test for continuous variables (two-sided tests). Cumulative mucositis rates were estimated by the Kaplan–Meier method and the corresponding curves were compared by the log-rank test. This study was approved by local and institutional ethical committees.

Results

Patients entered this trial from April 1991 to November 1993. A total of 105 patients were randomised, 53 in the sucralfate arm and 52 in the placebo arm. Three patients could not be included in the analysis because of recurrence of haematological disease after randomisation (two in sucralfate and one in placebo group). The analysis was thus performed on 51 patients in each group. Baseline characteristics in the two groups were similar (Table 1), in particular the number of previous therapies and the type of conditioning regimens. Although the incidence of mucositis of any grade was similar in both arms (84% in the sucralfate arm versus 88% in the placebo arm), the proportion of patients with grade 3–4 oral mucositis was higher in the placebo group than in the sucralfate group (47% vs. 29%, P = 0.07). An elevated proportion of grade 3/4 mucositis was also observed in allografted patients (82% vs. 17% for autografted patients, $P < 0.0001$), and in patients treated by TBI (50% vs. 21%, $P < 0.01$). After adjustment on TBI (the sole stratification parameter), the P-value comparing the frequence of grade 3–4 mucositis in the sucralfate and the placebo arms was 0.06. Acute GvHD was diagnosed in 57% of patients (8 of 14) in the sucralfate arm and 47% (8 of 17) in the placebo arm, with upper digestive tract involvement in three cases (two cases in the sucralfate group and one case in the placebo group). The incidence of oral mucositis was not significantly influenced by acute GVHD and the growth factors administration.

Interestingly, we observed a highly significant decrease of the occurrence of diarrhoea in the sucralfate group (25% vs. 53%, P = 0.005). Finally, sucralfate treatment can favour the recovery of enteral alimentation, with, at the fourth week post-graft, a mean caloric intake of 647 Kcal in the sucralfate group compared with 409 in the placebo group (P = 0.04). No difference was noted concerning the duration of oral mucositis, the incidence of vomiting, gastrointestinal haemorrhage, or septicaemia, as well as the use of antibiotics, antivirals, and analgesic drugs (data not shown). The actuarial survival, evaluated from the first day of randomisation until bone marrow recovery, was similar in both groups.

Conclusion

In this prospective monocentric randomised study, the preventive administration of sucralfate appeared to efficiently diminish the discomfort induced by conditioning regimen of BMT, with less patients suffering from diarrhoea. A trend was also observed (P = 0.06) for a diminution of severe stomatitis. The difference between placebo and sucralfate groups concerning this endpoint was not as important as anticipated, because the rate of severe mucositis was lower than expected in the placebo group. This was probably due to the protective effects mediated by mechanical mouth washes with placebo solution that allow the repeated removal of drugs eliminated in the saliva. The impressive reduction of diarrhoea could appear as more surprising, but can be explained by the well established intestinal cytoprotector properties of swallowed sucralfate [4]. The overall results obtained in this preventive study confirm and extend what was observed in a previous randomised study testing sucralfate for the prevention of chemotherapy-induced mucositis, in which a significant reduction in oedema, erythema and ulceration was reported in a low number of evaluable patients receiving a combination of 5-fluorouracil and cisplatin [5]. In contrast, the results of a recent randomised double-blind study indicated that sucralfate was not effective to treat 5-fluorouracil stomatitis, without any difference between the investigational and the placebo arms [6]. However, in this last trial, sucralfate was not administered as a prophylactic procedure, but only in patients developing mucositis despite an effective preventive cryotherapy with ice chips [7]. Furthermore, stomatitis was evaluated by historical means and not in a prospective manner as in the present work.

In conclusion, although sucralfate is probably poorly active to treat established mucosal damage induced by cytotoxic drugs, it appears to be an effective drug for the prevention of severe oral and intestinal mucositis in patients treated by high dose chemotherapy (and TBI) before BMT. The long-term (several weeks) administration of sucralfate is difficult in this setting, due to the important nausea occurring after BMT. Further clinical research should determine whether a short-term (one or two weeks) prophylactic administration can also protect the patient from this severe side effect.

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Correspondence to:
Pierre-Yves Dietrich, MD
Hôpital Universitaire
Division d'Oncologie
1211 Genève 14
Switzerland
E-mail: pierre-yves.dietrich@hcuge.ch