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Papers

Prevention of Oral Mucositis in Patients Treated with High-dose Chemotherapy and Bone Marrow Transplantation: A Randomised Controlled Trial Comparing Two Protocols of Dental Care

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Between February 1986 and November 1989, 166 patients who were candidates for a bone marrow transplantation entered a randomised controlled clinical trial to compare limited oral hygiene care (LIM) and intensive oral hygiene care (INT) in the prevention of mucositis. Randomisation was stratified on the initial oral status (good vs. bad IOS). Intensive oral hygiene care included an initial treatment of dental lesions and tooth and gum brushing during aplasia. Limited oral hygiene care excluded preventive dental treatment and gingival and tooth brushing. Mucositis was classified as absent, mild, moderate or severe, according to the clinical aspects of the different sites in the mouth and to two scales of pain evaluation. Of the 150 evaluable patients (75 in each group), 134 developed moderate/severe mucositis (64 in the INT group and 70 in the LIM group) (log-rank test $P < 0.02$). The superiority of intensive oral care was observed both in patients with and without total body irradiation (TBI) and in patients with a good or bad IOS; the observed risk of mucositis was reduced by 70% in each of these four subgroups. Duration of moderate/severe mucositis was, although not significantly, lower in the INT group (17 days, S.D. = 12) than in the LIM group (19 days, S.D. = 13). The median time of mucositis occurrence was 11 days in the INT group and 9 days in the LIM group. Contrary to a widespread belief, the percentage of documented septicaemia was not higher in patients who underwent intensive oral care. We conclude that, although statistically significant, the superiority of intensive oral hygiene care is not clinically impressive. However, reservations concerning tooth-brushing during aplasia can now be lifted.
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INTRODUCTION

ORAL MUCOSITIS and oral complications during bone marrow transplantation are frequent consequences of high-dose chemotherapy and radiotherapy used in the treatment of cancer. This bothersome complication can be very painful and can obstruct or prevent speech, oral hygiene, chewing, swallowing and the oral intake of drugs. Furthermore, mucosal damage has been suspected to lead to infections in these immunodepressed patients. Consequently, many haematologists feel that tooth brushing is dangerous because it may give rise to infectious and hemorrhagic complications [1–6]. In addition, no curative treatment of mucositis has so far been demonstrated to be efficient. Mucositis can also be a dose-limiting factor and thereby decrease the effectiveness of conditioning chemotherapy. The NIH consensus conference emphasised minimising oral complications in order to optimise cancer treatment [7].

Many have believed that oral mucositis can be induced or worsened by a lack of oral hygiene including tooth brushing, from the onset of the conditioning therapy to the end of aplasia. We report here the results of a randomised controlled

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trial, whose aim was to compare the occurrence of oral mucositis and oral complications in patients treated with intensive tooth brushing and mouthwashes and in patients treated with mouthwashes only.

PATIENTS AND METHODS

Patients

Subjects eligible for inclusion were patients with a malignant disease hospitalised in the Haematological Department of the Institut Gustave Roussy, who were candidates for bone marrow transplantation (BMT). Patients of both sexes, over the age of 4 years were eligible for inclusion as long as they were not edentulous and could assume their own oral care. Informed consent was required of all eligible patients. Patients were only included once in the trial, either for a first or a second course of high-dose chemotherapy (HDC) and BMT. The initial evaluation for eligible patients, consisted of a complete initial oral examination including screening of caries, periodontal lesions, periapical disease, dental malpositions, misfitting protheses and periodontal pocket. The assessment of the initial oral status was based on several items: More than three caries concerning two different surfaces, two caries (or more) concerning three different surfaces or more, acute pulpal infection with or without periapical involvement, crowns and restaurations with overhanging margins, major teeth malpositions and presence of partially erupted wisdom teeth, teeth with periodontal pockets greater than 6 mm. As a result of this examination, patients were classified according to their initial oral status (IOS) as good IOS (no dental or periodontal lesion) or bad IOS (one dental or periodontal lesion or more).

Treatments

Patients fulfilling the enrolment criteria were randomly allocated by telephone, either to intensive oral hygiene care or to limited oral hygiene care, a few days before the beginning of the conditioning regimen with HDC and/or total body irradiation (TBI). Randomisation was balanced every 4 subjects and stratified on IOS.

The intensive oral hygiene care included (i) initial dental treatment: treatment of caries, extraction of severely-compromised teeth, scaling and motivation in mouth care; (ii) during aplasia: tooth and gum brushing with a toothbrush at least three times a day after meals; the recommended method of tooth-brushing associated the Bass sulcular technique and/or Charters' method according to the dental and periodontal status of the patient. Tooth brushing had to be interrupted if uncontrollable gum bleeding occurred. Oral hygiene care instructions were provided by the dentist in charge of the trial.

The limited oral hygiene care excluded (i) preventive dental treatment (except in the case of a life-threatening dental infection making tooth extraction imperative), (ii) gingival and tooth brushing.

Mouthwashes with chlorhexidine were performed at least five times daily in both groups.

Treatments had to be administered from the first day of the conditioning regimen until bone marrow recovery (granulocytes $> 0.5\ 10^9/l$).

Follow-up

The follow-up began on the first day of the conditioning regimen and was continued until bone marrow recovery. The patients' oral status was assessed according to Beck's classification [8] twice weekly by a skilled practitioner during the follow-up period and recorded on an evaluation form. The oral status was assessed according to the texture (coded 0–3), colour (coded 0–3) and moisture (coded 0–3) of the following: lips, tongue, oral mucosa, gums. Also considered in this evaluation were: saliva, ability to swallow and clinical signs of herpes or candida infection (each coded 0–3). Pain evaluation was performed separately by the patient and the physician on a 100 mm visual analogical scale. Moreover the patient was asked to define his pain with a five point numerical verbal pain scale (1 = no pain or not at all, 2 = mild or a little, 3 = moderate or average, 4 = strong or a lot, 5 = extreme or extremely). Oral microbial cultures were performed when an oral infection was suspected. Dental plaque, which reflects the frequency and the intensity of tooth brushing, was also recorded (coded 0–3) in order to evaluate compliance to treatments. As these evaluations could not be performed blindly because of dental plaque, a second practitioner recorded all the items of the oral status assessment for some patients, in order to test their reproducibility.

Criteria of assessment

The principal criterion of assessment was the occurrence and duration of moderate and/or severe mucositis during the follow-up period. Mucositis was classified as absent, mild, moderate or severe, as following: mucositis was considered severe when either speaking, chewing or swallowing was impossible and/or when two or more items describing oral status were coded 3, and/or when pain evaluation was comprised between 80 and 100 mm on the visual analogical scale. In other cases, when at least two items were coded 2 or 3 and/or when pain was scored between 40 and 80 mm, mucositis was considered moderate. Mucositis was considered absent when one item maximum was coded 2 and when pain was inferior to 40 mm. In all other cases it was considered mild.

The other criteria of assessment were (i) the occurrence and duration of a febrile episode (persistent pyrexia $> 38°C$ for at least 6 h), (ii) the incidence of documented septicaemia.

Sample size

It was estimated [9] that a minimum of 75 patients per group would be necessary to demonstrate a minimal difference of 30% in the rate of moderate and/or severe oral mucositis between the two groups, during aplasia (2-tailed test, $\alpha = 5\%$, $\beta = 5\%$, oral mucositis rate around 50%).

Statistical methods

Standard statistical methods were used for data analysis. Cumulative oral mucositis rates and other cumulative survival rates were estimated by the Kaplan–Meier method [10] and the corresponding curves were compared by the log-rank test [11]; 95% confidence intervals were calculated by the Rothman method [12]. Concordance studies were performed using the Kappa coefficient.

RESULTS

Patients entered the trial from February 1986 to November 1989. A total of 166 patients were randomised, 84 in the

*Table 1. Comparability of the two groups**

	Intensive	Limited
Number of patients	75	75
Males	61%	59%
Age† (years)	27 (12)	27 (12)
Diagnosis		
Chronic myeloid leukaemia	12%	11%
Acute myeloid leukaemia	17%	15%
Acute lymphoblastic leukaemia	19%	22%
Lymphoma	27%	24%
Germ cell tumour	20%	19%
Other	5%	9%
Good initial oral status	45%	48%

*No differences between the groups were statistically significant.
†Mean (S.D.).

*Table 2. Graft and follow-up characteristics**

	Intensive	Limited
Number of patients	75	75
Stomato-toxicity of HDC		
None	52%	48%
Mild	28%	29%
Severe	20%	23%
Total body irradiation	57%	57%
Interval between HDC and BMT†	6.8 (2.1)	7.0 (2.5)
Interval between HDC and aplasia†	7.4 (2.3)	6.6 (2.6)
Autologous BMT	61%	55%
Graft vs. host disease	21%	24%
Duration of aplasia†	24.9 (16.6)	26.1 (18.6)

*No differences between the groups were statistically significant.
†Days, mean (S.D.).

intensive care group (INT) and 82 in the limited care group (LIM). 16 patients were not taken into account in the analysis: 13 did not receive HDC (9 in INT group and 4 in LIM group), 2 (LIM group) could not be followed-up because the physician in charge was on holiday, and 1 patient died before the beginning of aplasia (LIM group). The analysis presented here thus concerns 75 patients in each group. Table 1 compares selected initial characteristics in the two groups. Table 2 describes the characteristics of the conditioning regimen and the graft.

The assessments of the two practitioners who evaluated the oral status during the follow-up were based on 62 evaluation forms in 39 patients. The degree of equivalence between the assessments was excellent for all the items recorded coded 0 to 3 ($10^{-5} < P < 0.02$). The kappa coefficient for mucositis was 0.70 ($P < 10^{-5}$) when coded 0 to 3 and 100% ($P < 10^{-5}$) when coded absent–mild vs. moderate–severe.

In order to study compliance, we compared the maximum level of dental plaque (coded 0–3) recorded from the beginning of the conditioning regimen until the occurrence of moderate/severe mucositis (or the end of the trial) in the two groups. The percentage of grade 0, 1, 2 and 3 was 39%, 46%, 13% and 1% in the INT group and 6%, 37%, 51% and 6% in the LIM group ($P < 10^{-4}$), respectively. The grade of dental plaque was also compared at various times after the beginning of the conditioning regimen; the percentage of patients with grade 0 was always greater than 60% in the INT group while it was always less than 22% in the LIM group. Compliance was also studied during mucositis; the maximum levels of dental plaque during mucositis were 30%, 28%, 31% and 11% in the INT group and 0%, 11%, 49% and 40% in the LIM group ($P < 10^{-5}$) for grades 0 to 3, respectively. 2 patients in the INT group had to discontinue tooth brushing because of a heavy spontaneous oral and nasal haemorrhage.

TBI appeared to be highly prognostic for the occurrence of moderate/severe mucositis (log-rank test $P < 0.001$, Fig. 1). On the contrary, no prognostic value was found for IOS among our data on both groups and in the control group analysed separately. Moreover, no association was found between graft vs. host disease and the occurrence of mucositis.

A total of 134 moderate/severe cases of mucositis was observed (64 in the INT group: 15 moderate and 49 severe, and 70 in the LIM group: 12 moderate and 58 severe). The median time of mucositis occurence was 11 days post HDC in the INT group and 9 days post HDC in the LIM group. The cumulative proportion (S.D) of patients with oral mucositis 7, 14 and 21 days after the conditioning regimen was 8% (3%), 68% (5%), 81% (5%) in the INT group and 16% (4%), 80% (5%), 93% (3%) in the LIM group (Fig. 2, log-rank test $P < 0.02$). Patients treated by intensive oral care had a reduced risk of developing moderate/severe mucositis of 70% compared to patients with limited oral care. When adjusted on TBI and IOS, the log-rank test was $P < 0.01$ ($\chi^2 = 6.8$). This efficacy of intensive oral care was observed both in patients with and

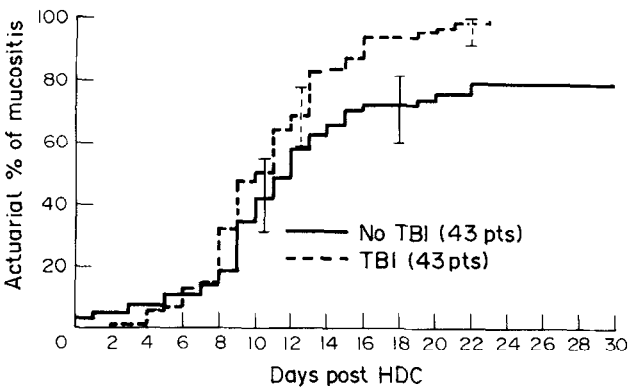

Fig. 1. Actuarial proportion of patients with moderate/severe mucositis according to total body irradiation.

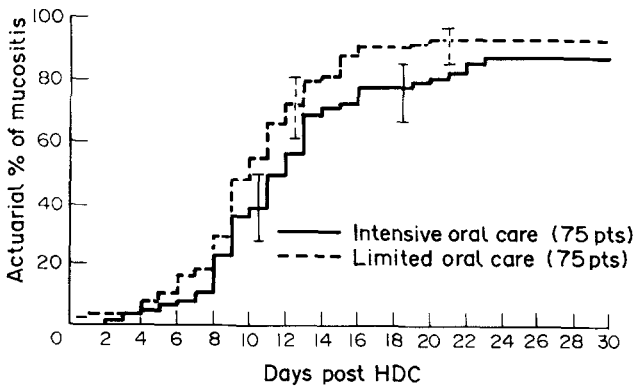

Fig. 2. Cumulative proportion of patients with moderate/severe mucositis according to treatment.

without TBI and in patients with a good IOS and a bad IOS: the risk of developing moderate/severe mucositis was reduced by 70% in each of these subgroups.

No difference was found in the mean duration (S.D.) of moderate/severe mucositis between the INT group (17 days [12]) and the LIM group (19 days [13]). This result remained unchanged when adjusted on TBI and IOS.

All patients but one in the INT group experienced bouts of fever during aplasia (log-rank test NS). The mean (S.D.) duration of fever did not differ between the INT group (13 days [10]) and the LIM group (15 days [12]). The incidence of documented septicaemia during aplasia was 17% in the INT group and 21% in the LIM group (log-rank test NS). On the other hand, the duration of fever was longer ($P<0.05$) in patients with TBI (16 days, S.D. = 12) than in patients who did not undergo TBI (12 days, S.D. = 9); no difference was found in the duration of fever between the good IOS patients (13 days, S.D. = 10) and bad IOS patients (15 days, S.D. = 12).

The actuarial survival, evaluated from the first day of randomisation, until bone marrow recovery was similar in the two groups (log-rank test NS).

DISCUSSION

Severe mucositis is a major cause of morbidity among patients undergoing high-dose chemo/radiotherapy followed by bone marrow transplantation. No curative treatment has been found for this very painful complication which can lead to dreadful discomfort. In 1985 a randomised controlled trial was initiated in the Institut Gustave Roussy to study the effect of initial dental treatment associated with reinforced tooth-brushing on oral complications during aplasia in these patients. By reducing mucositis, this approach was expected to decrease pain and bleeding, reduce local and general infections and allow these isolated patients to enjoy better psychological well-being by brushing their teeth regularly.

166 patients were enrolled in this trial. The sample size was estimated with a reference percentage of mucositis in patients without tooth brushing equal to 50%. This figure was chosen because the proportion of patients developing oral mucositis during aplasia varies between 40 and 70% in the literature [1–3, 13–19]. In fact, the observed actuarial proportion of patients with oral moderate/severe mucositis in the control group was 93% at 21 days in our study. This high figure can be explained by the fact that our patients all had HDC and also because our definition of mucositis included ulcerations, pain and dysphagia.

Patients who begin cancer chemotherapy with a good IOS have been described as at lower risk of mucositis and oral complications than patients with a bad IOS [20, 21]. Total body irradiation is also a well known prognostic factor of mucositis [22, 23]. Randomisation was stratified on IOS only, but as shown in Table 2, the percentage of patients who received TBI was the same in the two groups (57%). The analysis was adjusted for these two factors.

16 patients were excluded from the analysis (9 in the INT group and 7 in the LIM group). Of these, 13 did not receive HDC and 1 died before aplasia, so that they were not at risk for mucositis; thus the exclusion of these patients cannot be a source of bias.

Compliance with tooth brushing is difficult to assess on the basis of patients' verbal response. Dental plaque is considered one of the most reliable indicators of tooth brushing. When the percentage for each grade (0, 1, 2, 3), or the maximum grade until the occurrence of mucositis is taken into account, compliance can be considered satisfactory. After the onset of mucositis, dental plaque was significantly less intense in the INT group than in the LIM group; this suggests albeit surprisingly, that patients did not discontinue tooth brushing when mucositis occurred, in spite of pain.

As expected, TBI appeared to have a strong prognostic effect on the occurrence of mucositis. This result is in agreement with Chapko *et al.* [23] who found that the severity of mucositis and pain is associated with TBI.

The main result of this trial is a 70% reduction in the incidence of oral mucositis during aplasia in patients with intensive oral care compared with patients with limited oral care. No significant difference was noted in the duration of mucositis between the INT group (17 days) and in the LIM group (19 days). Contrary to a widespread belief [1–6], the percentage of infections and the percentage of documented septicaemia was not higher in patients undergoing intensive oral care. We suggest that the 70% decrease in the risk of mucositis in the INT group resulted from the decrease of gingival inflammation, which is itself at the origin of the mucositis. This gingival inflammation is probably reduced both by the initial dental treatment of tooth lesions and by tooth and gum brushing.

No randomised controlled trial comparing initial dental treatment vs. no initial dental treatment, or comparing intensive oral care during aplasia vs. no oral care has been published in the literature. One of the first studies on this topic was performed by Beck [8] who compared 22 patients with an oral care-protocol and 25 control patients in a non-randomised trial; results showed a significant improvement in oral status with oral hygiene care. Most authors usually recommend initial dental treatment [20–22, 24] in patients undergoing BMT. With respect to oral care during aplasia, most dentists and oncologists [1–5] prefer to exclude tooth-brushing when the patient's granulocyte blood count drops below 0.5×10^9/l and/or platelet count drops below 20×10^9/l because of the risk of bacteraemia and bleeding. Some accept to continue routine oral hygiene after the beginning of aplasia, only if initial preventive dental treatment has been performed [25, 26]. Lastly, the attitude to adopt has not been clearly indicated by others [6, 27].

The results of our trial may be criticised on the grounds that the assessment of mucositis is based on subjective criteria that cannot be measured blindly, because of dental plaque. However, the degree of equivalence between the assessments of mucositis of the two practitioners was excellent.

In conclusion, in this randomised trial, intensive oral care proved to be efficient in decreasing the occurrence of oral mucositis in patients treated with high-dose chemotherapy. It is impossible to dissociate the effects of initial dental treatment and intensive oral care during aplasia; however, the lack of a prognostic value for initial oral status on the occurrence of mucositis in the control group suggests the efficacy of tooth-brushing in the prevention of mucositis. Although statistically significant, the superiority of intensive oral hygiene care is not clinically impressive. However, the ban on oral care during aplasia can now be lifted.

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