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Phase II Study of Polymyxin B, Tobramycin, and Clotrimazole to Prevent Oral Irradiation Mucositis

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SUMMARY Colonization of the oral mucosa by gram-negative organisms and/or fungi is theorized to be an etiologic factor in severe mucosal reactions in patients receiving radiation to treat head and neck cancers. Patients treated with altered fractionation schedules have high rates of confluent mucositis, which can be slow to heal and can on occasion disrupt the continuity of the radiation course, with possible detrimental effects on outcome. It has been proposed that antimicrobial agents directed at these organisms can alleviate the severity of the mucosal reactions. We studied the use of a suspension of polymyxin B and tobramycin in conjunction with a clotrimazole troche in patients receiving radiotherapy with altered fractionation schedules to the oropharynx or oral cavity. Thirty-seven patients were enrolled in the trial. Radiation doses ranged from 63 to 77 Gy over 5–7 weeks. The rate of confluent mucositis in the entire group was 84%. This was not significantly different ($P > 0.1$) from a rate of 85% seen in an historical control group of 79 patients treated with our concomitant boost regimen. Possible reasons for the apparent ineffectiveness of this antibacterial-antifungal regimen are discussed. *Radiat Oncol Invest 1996;4:23–26.*

Key words: mucositis, radiotherapy, polymyxin B, tobramycin, head and neck cancer

INTRODUCTION

A common side effect during radiation therapy for cancers of the head and neck region is an acute mucositis. This reaction can vary in intensity and, if severe, can not only be very painful to the patient but may cause interruption of the treatment, with a detrimental effect on tumor control. The severity of acute mucositis is related to the rate of dose accumulation and is the major limiting toxicity with accelerated fractionation schedules. In our own experience with the concomitant boost technique, treating primary cancers of the oropharynx, the incidence of confluent mucositis of the irradiated tissues was greater than 85% [1].

Although all mucous membranes react to radiation, this inflammatory response is thought to be exacerbated by superinfection with microorganisms. Reports have demonstrated colonization of the oropharynx with gram-negative bacilli and fungi [2]. Several studies [3–7] have been conducted using antimicrobial and/or antifungal rinses to reduce radiation mucositis, with varying degrees of success. Spijkervet et al. [8] described a lozenge consisting of polymyxin E, tobramycin, and amphotericin B used for reducing mucositis in patients with oral cavity cancers treated with conventionally (once daily) fractionated radiation. The authors noted in a test group of 15 patients a decrease in

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Table 1. Grading System for Mucosal Reactions

Grade	Definition
0	No reaction
1	Erythema
2	Patchy mucositis; formation of pseudomembranes less than 1 cm
3	Confluent pseudomembrane formation covering less than one-half the irradiated volume
4	Confluent pseudomembrane formation covering more than one-half the irradiated volume

the incidence of severe mucositis compared with a historical control group treated with placebo or chlorhexadine 0.1%. Encouraged by this report as well as positive anecdotal reports, we tested a similar combination of drugs in a study designed to reduce the high incidence of confluent mucositis seen in our patients treated with accelerated fractionation regimens.

MATERIALS AND METHODS

The antibiotic rinse consisted of a suspension containing a mixture of polymyxin B (2 mg/5 ml) and tobramycin (1.8 mg/5 ml). The rinse was compounded with 400 mg polymyxin B, 360 mg tobramycin, 1 g sodium benzoate, 5 g methylcellulose 4000, 200 ml Syrpalta, and sufficient sterile water to bring the volume to 1 liter. Patients were instructed to swish and swallow 1 teaspoon of the rinse four times daily throughout their course of radiation and for an additional 2 weeks following completion of their therapy. In addition to the rinse, patients used a clotrimazole troche three times per day for the duration of radiation and an additional 2 weeks. Patients were examined weekly, and the grade of mucositis was scored (Table 1). This grading system had been for our historical control group. Patients who developed grade 3 and 4 mucositis were considered treatment failures, and the drugs were discontinued.

Thirty-seven patients, all with biopsy proven squamous cell carcinomas, were entered into the study. All had planned treatment with altered fractionation regimens consisting of twice per day irradiation for part or all the treatment. Three patients had surgical resections, two with oral cavity cancers and one with a base of tongue primary cancer. They received postoperative radiotherapy on an accelerated fractionation protocol to doses of 63 Gy in 35 fractions over 5 weeks. The remaining 34 patients were to be treated with radiation only. Three patients had nasopharyngeal primary cancers, and the remaining 31 had primary lesions of the oropharynx (Table 2). These patients were treated with one of three different radiation fractionation regimens. The concomitant boost regimen consisted of 72 Gy in 42 fractions over 6 weeks, with twice per day treatment reserved for the final 12 days of treatment [1]. The hyperfractionation regimen delivered doses of 76–80 Gy in 66–68 fractions delivered over 7 weeks. The third regimen was an accelerated split-course regimen that delivered 67 Gy in 42 fractions over 6 weeks, with a 2 week rest period during the treatment. The latter two regimens used twice per day treatment for the entire duration.

Patients were treated with parallel opposed portals to the primary tumor (or operative bed) and to the upper neck. A separate field was used to treat the lower neck. Field reductions to the treated mucosal volume were planned after 38–55 Gy, depending on the fractionation regimen. All patients were treated with megavoltage equipment.

The experimental group was compared with a historical control group of 79 oropharyngeal and nasopharyngeal cancer patients treated with radiation only using the concomitant boost regimen described above. During radiation these patients in the historical control group were given instructions on maintaining oral hygiene, including rinsing with a baking soda solution multiple times per day. Systemic narcotic analgesics and topical viscous xylocaine and/or topical carafate suspensions were used to alleviate symptoms from their mucosal reactions when these were evident. Sixty-seven (85%) of these patients developed grade 3 or 4 mucositis. The endpoint tested was the incidence of confluent mucositis in the experimental group. The χ^2 test was used to test for statistically significant differences bewteen the two groups.

RESULTS

All 37 patients completed their planned radiation. One of the three patients treated postoperatively refused twice per day treatment and received his planned dose of 63 Gy over 7 weeks. The 34 patients who received definitive radiation alone were distributed among the three different fractionation regimens as follows: concomitant boost, 24 patients; hyperfractionation, six; accelerated split course, four. All patients were treated with shrinking field techniques. The median area of mucosa encompassed in the initial large fields was 60.3 cm^2 (range 38–104 cm^2). The doses to these larger fields ranged from 38 to 55 Gy, depending on the fractionation schedule. The median area of the boost fields that received full doses (63–80 Gy) was 42 cm^2 (range 27–77 cm^2).

Four patients discontinued the drugs during

Table 2. Patient and Tumor Characteristics

Characteristic	Historical group (n = 79)	Experimental group (n = 37)
Age range (years) [median]	19–84 [60]	39–84 [61]
Male:female (male %)	58:21 (73)	27:10 (73)
Site of primary disease (%)		
Oropharynx	72 (91)	32 (87)
Base of tongue	17	8
Tonsil	31	19
Soft palate	16	3
Pharyngeal wall	8	2
Nasopharynx	7 (9)	3 (8)
Oral tongue	0 (0)	2 (5)
T stage (%)		
T_2	41 (52)	21 (57)
T_3	33 (42)	14 (38)
T_4	5 (6)	2 (5)

Table 3. Mucosal Reactions

Group	Mucosal grade (%)		
	2	3	4
Experimental (n = 33)	5 (15)	11 (33)	17 (52)
Historical control (n = 76)[a]	9 (12)	17 (22)	50 (66)

[a]Three patients unscored.

their radiation. Thirty-one (84%) patients developed a confluent mucositis. Table 3 details the incidence of mucositis by grade. The difference between rates of confluent mucositis between the experimental and the historical control groups was not significant ($P > 0.1$). Both patients with oral cavity carcinomas developed grade 3 mucositis.

Side effects were minimal. Sixteen patients developed nausea. Despite clotrimazole use, four patients developed oral candidiasis.

DISCUSSION

We did not see significant differences in the rate of confluent mucositis using our antibacterial/antifungal regimen. These results were disappointing in light of the favorable trial reported by Spijkervet et al. [8]. However, there were several differences between these trials that may account for the different results.

Our drug preparation was different. The antibiotics we used were in a suspension rather than a lozenge, and our antifungal agent was clotrimazole rather than amphotericin. Because these drugs are used as topical agents, it is possible that the shorter contact time of the suspension with the mucosa at risk made the suspension less effective than a lozenge. It is unlikely that the difference in antifungal agents accounted for the ineffectiveness of our regimen; candidiasis is not the major etiologic agent of adverse mucositis.

A second difference was our study group. All but two of our patients had pharyngeal lesions, so the tissues at risk were different. Topical treatment of the oropharnygeal mucosa is difficult to ensure with an oral rinse vehicle, and, regardless of the preparation, the mucosa may not have adequate exposure to the drugs. Additionally, gram-negative bacilli may not be as responsible for irradiation mucositis in the oropharynx as they are in the oral cavity, especially in patients who are not being treated postoperatively. Kaanders et al. [9] recently reported on their use of topical antimicrobials for patients irradiated to the oral cavity or oropharynx. Although less mucositis was seen in their oral cavity patients, a benefit from the use of antibacterial/antifungal lozenges in their oropharynx population was not seen. Our two patients with oral cavity primary cancers both developed grade 3 mucositis. Although grade 3 mucositis was considered a failure in this study, we were pleased with only this severity of reactions in patients receiving 63 Gy in 5 weeks to the oral tissues.

The last main difference was that our study used unconventional fractionation schedules. Patients receiving these schedules are expected to have a high degree of mucositis, with rates higher than those expected with conventional treatment [10]. These schedules may create degrees of denudation of the mucosa such that superinfection may not be as important a factor in the etiology of confluent mucositis. Because the endpoint was severity of mucositis, and not infection, microbiologic studies were not performed.

As accelerated radiation schedules become more popular, methods to combat the severe mucosal reactions must be developed. Some antibiotic trials have been more promising [4,8,9]. Our suspension was ineffective in reducing the incidence of severe oropharyngeal mucositis. Further development and testing should be done to validate the use of topical antibiotics in these settings before they are used routinely.

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