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## Use of Metronidazole Gel to Control Malodor in Advanced and Recurrent Breast Cancer

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Intolerable malodor emanating from ulcerated tumors as a result of anaerobic infection is a serious problem in the management of advanced and recurrent breast cancer. Metronidazole can control this malodor, but its oral use may cause adverse reactions. We therefore formulated a metronidazole gel, since no equivalent preparation is commercially available in Japan, and used it in five female patients (four with advanced cancer and one with recurrent cancer) admitted to our hospital between March 1994 and July 1995. The patients were aged between 47 and 71 (median: 59) years, and the duration of morbidity in the four patients with advanced cancer ranged from 10 months to four years. In three patients, the tumors were larger than 10 cm × 10 cm. Metronidazole gel was applied to the surface of ulcerated tumors once or twice daily. Independent assessments by the patient, doctor and nurse were unanimous, and revealed that the malodor was alleviated in one patient after three days, and removed in four patients after two to five (median: four) days of metronidazole gel treatment. Culture of swabs showed a decrease or disappearance of anaerobic colonies. Adverse reactions characteristic of metronidazole did not occur. The topical use of metronidazole in a gel form will improve the quality of life for patients with malodorous ulcerated tumors and facilitate intensive treatment of the underlying disease.

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### Introduction

Ulcerated tumors, as well as pressure sores, are susceptible to mixed bacterial infection and tend to produce an unpleasant odor.<sup>1,2</sup> Anaerobes are believed to be the causative bacteria of such malodor.<sup>2-4</sup> Among various agents effective against anaerobic infection, oral metronidazole has been widely used to control the malodor of pressure sores, breast cancer, head and neck tumors and other miscellaneous cancers.<sup>3-6</sup> Despite its proven efficacy, however, oral metronidazole may cause adverse reactions such as gastrointestinal disturbance (e.g., nausea, anorexia, vomiting and diarrhea), leukopenia and peripheral neuropathy.<sup>7</sup> Many investigators have therefore attempted to formulate topical

metronidazole preparations in solution or gel form in an attempt to decrease the incidence of the above adverse reactions.<sup>8-10</sup> These formulations have proved effective against anaerobic infection and resulting malodor. As these formulations are not yet commercially available in Japan, we formulated a metronidazole gel and used it to treat patients with ulcerated and malodorous breast cancer to clarify the nature of the associated bacterial infection and to evaluate the clinical and bacteriological effects of the gel.

### Materials and Methods

#### Formulation

We prepared 0.8% metronidazole gel using the following procedure. (1) Weigh 0.8 g of metronidazole (Tokyo Chemical Industry Co., Ltd., Tokyo). (2) Add 10 ml of propylene glycol (Koso Chemical Co., Ltd., Tokyo) to produce gelation. (3) Sufficiently disperse the gel in a water bath. (4) Add

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88 ml of warmed 1% carboxypolyethylene, (Mitsuya Chemicals Co., Ltd., Tokyo) to produce further gelation. (5) Heat and stir at a temperature lower than 70°C to dissolve the preparation completely. (6) Cool spontaneously to a temperature lower than 40°C. (7) Stir and gradually add 2 ml of 10% sodium hydroxide to neutralize the mixture. The metronidazole gel thus prepared is colorless, odorless and transparent.

### Patients

Five female patients with breast cancer were admitted to our hospital between March 1994 and July 1995. They were aged between 47 and 71 (median: 59) years. The disease duration was between 10 months and four years and had advanced to Stage IV in four patients. The remaining patient had recurrent cancer. Tumor size exceeded 10 cm × 10 cm in three patients (Table I). The tumors were ulcerated and malodorous in all patients instead of usual care.

### Administration

A dressing spread with metronidazole gel was applied to the ulcerated lesions once or twice daily. Systemic administration of antibiotics was prohibited during the study.

### Clinical Observation

The patient, doctor and nurse independently recorded the date on which malodor disappeared after use of the metronidazole gel. Furthermore, the doctor observed each patient for adverse reactions during the use of the gel.

### Bacteriological Examination

Before application of metronidazole gel and on the day when malodor disappeared, the swabs from the ulcerated tumors were cultured anaerobically and aerobically at 37°C for 48–72 h using Gifu University-prescribed medium and blood agar, respectively. Anaerobes were identified using a Rapid ANA II System (Innovative Diagnostic Systems, Inc., GA). Aerobes and facultatives were identified using an API 20 system (Bio Mérieux SA, Marcy-l'Etoile, France). Some clinically isolated anaerobes were examined for their sensitivity to metronidazole.

## Results

### Malodor

The three parties' assessments were unanimous: malodor disappeared in four patients with advanced cancer two to five (median: four) days after the start of metronidazole gel treatment. This medica-

tion was continued in three of the four patients until the day of death or mastectomy, and is still being continued in one patient. Malodor was alleviated in the remaining patient with recurrent cancer on day 4 of metronidazole gel treatment, but the patient died of the underlying disease on day 7 before disappearance of the malodor (Table I).

### Bacteriological Findings

Aerobes, anaerobes and facultatives were present in all patients before metronidazole gel treatment, and bacteriological examinations were performed in four of the five patients after the treatment. Aerobes and facultatives remained almost unchanged. However, anaerobic colonies disappeared or were decreased in the four patients after the malodor had been removed or alleviated by the drug. Sensitivity tests were performed for *Peptostreptococcus* and an unidentified anaerobic gram-negative rod isolated from Case 5. The minimal inhibitory concentrations (MIC) of metronidazole for these clinical isolates were very low (Table II).

### Adverse Reactions

Despite its long-term use (range: 6–131 days, median: 37 days), the metronidazole gel did not cause adverse reactions in any of the patients.

## Discussion

Sparrow *et al.* and Ashford *et al.* used metronidazole tablets to control malodor in patients with breast cancer.<sup>5,6</sup> They employed independent assessments by the patient, doctor and nurse to confirm that the effect of metronidazole on malodorous tumors was not a placebo response or the result of observer bias. We also adopted the same assessment method and confirmed the previous findings that metronidazole gel could reduce malodor in ulcerated tumors shortly after the start of administration.

Bacteriological investigations revealed that the ulcerated tumors in our patients were infected by aerobes, anaerobes and facultatives. Aerobes and facultatives were still present after metronidazole gel treatment. However, the colonies of all anaerobes isolated before metronidazole gel treatment disappeared or were decreased on the day when malodor was removed or alleviated. This corroborated the previous findings that anaerobes were responsible for the malodor of ulcerated tumors.

Among various anaerobes, *Bacteroides* sp. has been most frequently detected in ulcerated and malodorous tumors. Other causative anaerobes of malodor include *Fusobacterium* sp., *Peptococcus* sp. and *Peptostreptococcus* sp.<sup>1,2</sup> Except for *Pepto-*

## METRONIDAZOLE GEL FOR TUMOR MALODOR

Table I. Patients Studied and Clinical Course after Metronidazole Gel (MG) Treatment

Case	Age (yr)	Stage	Tumor size (cm)	Time until treatment	Malodor*		Days of MG treatment	Present status of the patient
					After MG treatment	Day required to remove/alleviate		
1	52	T4bN2M1 (Stage IV)	4 × 3	12 mo	removed	4	82	Died <sup>†</sup>
2	59	local recurrence	5 × 4	—	alleviated	3	6	Died <sup>†</sup>
3	47	T4bN1M1 (Stage IV)	11 × 10	4 yr	removed	4	131	Mastectomized
4	67	T4bN3M1 (Stage IV)	12 × 10	2 yr	removed	5	37	Died <sup>†</sup>
5	71	T4bN3M1 (Stage IV)	19 × 17	10 mo	removed	2	30	Under treatment

\* , based on unanimous assessment by the patient, doctor and nurse; † , cause: underlying disease.

Table II. Bacteria in Ulcerated Tumors before and after Metronidazole Gel Treatment

	Case 1	Case 2	Case 3	Case 4	Cases 5
<b>Aerobes</b>					
<i>Pseudomonas stutzeri</i>	+ /NE				
<i>Pseudomonas aeruginosa</i>		3+ /3+		3+ /3+	
<i>Acinetobacter lwoffii</i>			2+ /2+		3+ /-
<i>Acinetobacter baumannii</i>					- /2+
<b>Facultatives</b>					
<i>Staphylococcus aureus</i>		+ /+	2+ /2+		2+ /+
<i>Staphylococcus epidermidis</i>	+ /NE				
<i>Streptococcus</i> sp.	+ /NE			3+ /3+	
<i>Providencia rettgeri</i>				3+ /3+	
<i>Corynebacterium</i> sp.	2+ /NE		3+ /3+		3+ /3+
<b>Anaerobes</b>					
<i>Bacteroides fragilis</i>		2+ /+	3+ /-		
<i>Peptostreptococcus</i> sp.	2+ /NE				2+ /- <sup>†</sup>
<i>Veillonella</i> sp.				3+ /-	
<i>Fusobacterium</i> sp.					2+ /-
Gram-negative rod*				3+ /-	2+ /- <sup>‡</sup>

3+,  $10^7 - 10^8$  colony forming unit (CFU)/ml (whole of dish); 2+,  $10^3 - 10^6$  CFU/ml (half of dish); +,  $10^2 - 10^3$  CFU/ml (part of dish); -, not detected; NE, not examined; \*, not identified; †, minimal inhibitory concentration (MIC) 0.78 µg/ml; ‡, MIC 0.2 µg/ml.

*coccus* sp., we isolated not only the above anaerobes but also *Veillonella* sp. in this study. Anaerobes are normally an avirulent component of the resident flora, but become virulent in immunocompromised hosts. Necrotic tumor tissues resulting from inadequate blood supply are a favorable medium for these kinds of bacteria. Lipid decomposed by aerobes and facultatives provides an energy source for anaerobes. Catabolism of lipid produces acetic, propionic, isobutyric, butyric, isovaleric, and valeric acids. Gas chromatography suggests that these volatile fatty acids, except for acetic acid, are responsible for this type of malodor.<sup>4)</sup>

The potency of metronidazole is partly supported by our finding that the clinical isolates of *Peptostreptococcus* sp. and an anaerobic gram-negative rod were highly sensitive to metronidazole *in vitro*. On the other hand, the safety of metronidazole gel

is documented in the product information. It states that the serum concentration of metronidazole reached a maximum of 66 ng/ml in one patient when metronidazole gel was administered topically at a dose of 1 g (equivalent to 7.5 mg of metronidazole) to the face of 10 rosacea patients. This concentration is about 100 times lower than that after single oral administration of a 250-mg tablet of metronidazole.<sup>11)</sup>

We conclude that metronidazole gel benefited our patients, relieving them from their distressing malodor and making it possible for them to receive intensive care for the underlying disease without fear of adverse reactions due to metronidazole. This metronidazole gel formulation deserves wider use in patients with ulcerated and malodorous breast cancer.

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