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Anaerobic Infection in Cancer Patients: Comparative Evaluation of Clindamycin and Cefoxitin

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Clindamycin and cefoxitin with or without gentamicin were administered to cancer patients having localized infections presumably caused by anaerobic pathogens. The rates of favorable response were 89% in patients receiving clindamycin alone and 78% in patients receiving cefoxitin alone. When the total experience is considered (clindamycin or cefoxitin with and without gentamicin), 20 of 24 patients (83%) responded to clindamycin and 18 of 22 (82%) responded to cefoxitin. Both therapies were well tolerated. Clindamycin was found to be more effective than cefoxitin in eradicating the offending anaerobic pathogens from the site of infection. Aerobic pathogens were frequently isolated along with anaerobes from the infectious sites in this series; their susceptibility or resistance to clindamycin or cefoxitin did not influence the therapeutic response.

In recent years, emphasis has been placed on infections caused by anaerobic bacteria, especially those belonging to the *Bacteroides* group of bacilli. Although patients with cancer do not present a very high incidence of septicemia caused by anaerobic bacteria (2% of all septicemias) (5), *Bacteroides* sp. and other anaerobic pathogens can often be isolated from localized infections in this type of patient. It may be suspected that these anaerobic bacteria have some pathogenic role, although its precise importance may be difficult to assess. As a matter of fact, aerobic pathogens, especially gram-negative rods, are frequently found at the same site with the anaerobic microorganisms. The respective role of aerobic and anaerobic microorganisms in the genesis of localized infections to cancer patients is thus unclear. However, antibiotics such as clindamycin and tinidazole, which are especially active against anaerobes, are effective in wound infections in cancer patients from which anaerobic and aerobic bacteria can be isolated (8).

To investigate further the role of anaerobic bacteria in the pathogenesis of localized infections in cancer patients, we undertook the present study in which we compared clindamycin with cefoxitin, a newer broad-spectrum cephamycin which is effective in vitro against many aerobic and anaerobic strains of pathogenic microorganisms (2, 4). There is some suggestion that cefoxitin can also be effective clinically in anaerobic infections (3), but no comparative trials with a well-recognized therapeutic agent have been reported yet.

MATERIALS AND METHODS

Two groups of 25 patients, all of whom presented an underlying malignancy, were studied. Ultimately, anaerobic infection could be demonstrated microbiologically in 24 patients who received clindamycin and in 22 who received cefoxitin.

All of these patients are hospitalized at the Institut Jules Bordet, which is the clinical center for cancer therapy of Brussels University. All of the patients presented a similar degree of debilitation. No major differences in the underlying tumors were found among the two groups. Patients were admitted into the trial if they had a wound infection, an abscess, a tumor infection, or an infection of the tracheobronchial tree which was superimposed on a tracheostomy and was considered likely to be caused by anaerobic bacteria.

Patients received clindamycin or cefoxitin in a sequence predetermined by a random choice. During the first 72 h of therapy, clindamycin and cefoxitin were given intravenously. The dosage was 2 g three times daily for cefoxitin and 900 mg three times daily for clindamycin. Antibiotics were given in 5% glucose as 10-min infusions. Thereafter, the intramuscular route or the oral route (for clindamycin) was used in some patients. Addition of gentamicin (80 mg three times daily by the intramuscular or intravenous route) was allowed if the patient looked severely ill as the result of infection or when it was known that the patient was colonized at the site of infection by aerobic gram-negative bacilli.

Favorable clinical responses were considered to have been achieved when the initial clinical signs and symptoms related to the infection disappeared during therapy or improved markedly. Bacteriological cure was not considered necessary for a favorable clinical response. Mild intolerance to the antibiotics (not requiring discontinuation) and asymptomatic coloniza-

tion of the site of the infection were considered to be compatible with a favorable clinical response when indicated.

Aerobic and anaerobic cultures were obtained from the site of infection and from blood in all patients before and during therapy; in most patients these cultures were repeated after discontinuation of the antibiotics. Complete hematological examination and determination of blood urea nitrogen, creatinine, alkaline phosphatase, bilirubin, and oxalacetic-glutamic-pyruvic transaminase were performed before, during, and after therapy.

The identification of the various anaerobic microorganisms was determined according to the *Anaerobe Laboratory Manual* (7). Anaerobic conditions for cultures were provided by using the GasPak system (BBL Microbiology Systems). No anaerobic cabinet was used for the plating of clinical specimens or for the manipulations required by subculturing. In most cases, however, the clinical specimens were plated within a few minutes after collection. No special precautions were taken for specimen transport. Routine techniques were used for isolation and identification of aerobic microorganisms.

The susceptibility of the microorganisms to antibiotics was tested by the inoculum-replicating method of Foltz et al. (6), using Schaedler broth (BBL) with agar plates containing twofold dilutions of the antibiotics to be tested. The culture medium used for testing the susceptibility of the strains of *Bacteroides melaninogenicus* contained, in addition, 5% sheep blood. The inoculum consisted of an overnight culture of the microorganisms in peptone-yeast-glucose broth, prepared as indicated by the *Anaerobe Laboratory Manual* (7) (approximately 10^7 microorganisms per ml). The microorganisms were inoculated onto the surface of the agar with an automatic inoculating apparatus in a volume of approximately 0.003 ml. The plates were incubated for 48 h under anaerobic conditions at 37°C and then examined for evidence of growth. The lowest concentration at which no macroscopic growth could be seen on the plates was considered to represent the minimum inhibitory concentration (MIC).

Anaerobic and aerobic pathogens were considered to be resistant in vitro if the MIC was more than 1 μg/ml for clindamycin and more than 3 μg/ml for cefoxitin and gentamicin.

RESULTS

The clinical characteristics of the population of patients studied are summarized in Table 1. The patients in the two groups were comparable from the point of view of age and sex. All of them had an underlying neoplastic disease, and many had other associated diseases. The distribution of the type of cancer and other diseases was similar in both groups. The distributions of the different types of infections were almost identical in the two groups; infections of skin and soft tissues were frequently associated with ulcerated tumor, and surgical wound infections were found mainly in patients who underwent surgery for colonic or gynecological surgery.

TABLE 1. *Clinical characteristics*

Group	General features				No. with the following types of infection:			No. with the following clinical characteristics:				Mean no. of days before therapy
	No. of patients	Mean age (years)	No. of males	No. of females	Tracheostomy	Skin and soft tissues	Surgical wounds	Moderate infection	Severe infection	Temp of >38.5°C	Leukocytosis (>10,000)	
Clindamycin treated												
Total	24	61.5	14	10	5	15	4	19	5	3	11	6
Favorable response	20	61.5	11	9	4	13	3	15	5	3	9	
Cefoxitin treated												
Total	22	60.7	13	9	6	11	5	19	3	2	10	3.5
Favorable response	18	59.8	11	7	4	10	4	15	3	2	8	

Most of the infections treated were moderately severe and superimposed on some chronic pathological process, such as a tumor, a tracheostomy, or a complicated wound; in five clindamycin-treated patients and in three cefoxitin-treated patients the infections were severe enough to be considered life-threatening. Very high fevers (>38.5°C) were rarely seen in this series; elevated white cell counts were observed in about 50% of the patients. Almost all the specimens obtained for microbiological evaluation from the site of infection were grossly purulent and presented an offensive smell which disappeared as a rule very often after the onset of treatment in those patients who responded. As a matter of fact, the disappearance of the unpleasant smell was the first indication of a favorable outcome in most patients.

No difference in outcome was observed in relation to the clinical characteristics or to the type of infection considered here. It is recognized, however, that the subgroups were very small.

Table 2 indicates the microbiological characteristics of the infections studied here. Gram-negative anaerobic rods were responsible for most infections, *Bacteroides fragilis* and *B. melaninogenicus* being the most frequent. No specific relationship between the site of infection and the type of offending pathogen could be seen. Aerobic microorganisms were associated with anaerobes at the site of infection in 20 patients who received clindamycin and 19 patients who received cefoxitin; in the clindamycin group all of these aerobic microorganisms were gram-negative bacilli (mostly *Escherichia coli, Proteus* sp., *Pseudomonas aeruginosa* and *Klebsiella* sp., in decreasing frequency), but in the cefoxitin group six patients had also gram-positive cocci (*Staphylococcus aureus* in four cases; *Diplococcus pneumoniae* and *Streptococcus faecalis,* each in one case) along with aerobic gram-negative bacilli (mainly *E. coli* and *Proteus mirabilis*) at the site of infection.

Susceptibilities of the pathogens isolated are also indicated in Table 2. All of the anaerobic strains isolated in the clindamycin-treated patients were susceptible to clindamycin in vitro; on the other hand, four strains of *B. fragilis* isolated from four different cefoxitin-treated patients were resistant to cefoxitin. As far as the aerobic gram-positive cocci are concerned, 5 of 6 gram-positive cocci were susceptible to cefoxitin (MIC, <3 μg/ml), as were 10 of 13 of the gram-negative microorganisms; thus, 4 aerobic strains isolated in the cefoxitin-treated patients were resistant to cefoxitin. All of the gram-negative bacilli isolated in the clindamycin-treated patients were resistant to clindamycin (MIC, >1 μg/ml).

However, all of the gram-negative bacilli isolated in this series were susceptible to gentamicin (MIC, ≤3μg/ml).

Table 3 indicates the clinical and microbiological results observed here. Overall evaluation shows that 20 of 24 patients (83%) responded to clindamycin and 18 of 22 patients (82%) responded to cefoxitin; among the patients who received clindamycin or cefoxitin alone, 16 of 18 (89%) responded to clindamycin and 11 of 14

TABLE 2. *Microbiological characteristics*

Organism(s)	Clindamycin-treated patients		Cefoxitin-treated patients	
	Total no.	No. giving favorable response	Total no.	No. giving favorable response
Type(s) of anaerobes				
B. fragilis	5	3	6	6
B. melaninogenicus	9	8	3	3
Fusobacterium sp.	0	0	2	1
B. fragilis + *B. melaninogenicus*	6	6	8	6
B. melaninogenicus + peptostreptococci	1	1	0	0
B. melaninogenicus + *Fusobacterium* sp.	3	2	3	2
Associated aerobes				
Gram-positive cocci	0	0	6	6
Gram-negative rods	20	18	13	10
Susceptibility to therapy				
Aerobes resistant to clindamycin	20	18		
Aerobes resistant to cefoxitin			4[a]	4[a]
Anaerobes resistant to clindamycin	0	0		
Anaerobes resistant to cefoxitin			4[b]	4[b]

[a] One *S. faecalis* and three *P. aeruginosa.*
[b] Four *B. fragilis.*

TABLE 3. *Clinical and bacteriological results*

Result	No. showing result with:			
	Clindamycin alone (n = 18)	Clindamycin + gentamicin (n = 6)	Cefoxitin alone (n = 14)	Cefoxitin + gentamicin (n = 8)
Clinical				
Cure	13	2	8	6
Improvement	3	2	3	1
Failure	2	2	3	1
Deaths	1	2	2	2
Bacteriological				
Elimination of the initial pathogen	15	3	6	4
Colonization	4[a]	6[b]	4[c]	5[d]
Superinfection	4[e]	0	2[f]	1[g]

[a] *P. aeruginosa* + *S. faecalis*, 1; *S. aureus*, 1; *P. aeruginosa*, 1; *S. faecalis*, 1.
[b] *P. aeruginosa*, 3; *B. fragilis*, 2; *B. fragilis* + *P. aeruginosa*, 1.
[c] *Enterobacter* sp. + *P. aeruginosa*, 1; *P. aeruginosa*, 2; *B. fragilis* + *P. aeruginosa*, 1.
[d] *E. coli*, 1; *P. aeruginosa*, 2; *S. faecalis*, 1; *Enterobacter* sp., 1.
[e] *P. aeruginosa*, 2; *S. aureus*, 1; *P. mirabilis*, 1.
[f] *P. aeruginosa*, 1; *B. melaninogenicus*, 1.
[g] *P. aeruginosa*, 1.

(78%) responded to cefoxitin. No deaths could be attributed directly to progressive sepsis, although in some cases uncontrolled infection might have contributed to the fatal outcome. Elimination of the anaerobic pathogen considered to be responsible for the infection treated was achieved in 15 of 18 patients (84%) receiving clindamycin alone and in 6 of 14 patients (42%) receiving cefoxitin alone. Among the patients who received clindamycin alone, the offending pathogen was not eliminated in three patients, but only one of these did not respond to therapy. In the other group, the initial pathogens persisted in six patients; in two other patients, some of the initial anaerobic strains disappeared during therapy with cefoxitin but others persisted. Among the three clinical failures among the patients who received cefoxitin alone, two were associated with a failure to eradicate the anaerobic pathogen from the site of infection. There was a relationship between the eradication of the offending pathogen and the clinical outcome; in five patients who failed to respond to clindamycin or cefoxitin alone, elimination of the pathogen from the site of infection was achieved only in two (1 in each group). Among 27 patients who responded to clindamycin or cefoxitin, elimination of the offending pathogen was achieved in 19 (63%).

As already mentioned, all of the anaerobes isolated from patients who received clindamycin were susceptible to that antibiotic (MIC, $\leq$1 μg/ml). On the other hand, of 14 patients receiving cefoxitin alone, 3 had strains resistant to it. In all cases, the pathogen was *B. fragilis*, with an MIC of $\geq$50 μg/ml. One of these patients failed to respond to therapy, and the pathogen persisted at the site of infection; the MIC and the minimal bactericidal concentration for cefoxitin were more than 200 μg/ml in that case. The two other patients were considered clinical cures, but the resistant microorganism persisted at the site of the infection; in those two patients the MICs and minimal bactericidal concentrations were 50 μg/ml. Asymptomatic colonization of the site of the initial infection occurred frequently in this series and can probably be explained by the local pathological conditions present in all of these patients. Superinfection, mostly by aerobic microorganisms, occurred in four clindamycin-treated patients and in three cefoxitin-treated patients; in four patients, *P. aeruginosa* was responsible for this superinfection.

Untoward effects of therapy were not frequently found in this series. Pain at the site of intramuscular injection was reported by four patients receiving cefoxitin and by one patient in the other group. A cutaneous rash, presumably due to the antibiotic, was seen in two clindamycin-treated patients. No changes that could be attributed to the study drugs were seen in the results of the laboratory tests. In five patients receiving clindamycin or cefoxitin alone, a transient rise of the creatinine level was observed. The initial creatinine values were 1.3 and 0.6 mg/100 ml for the clindamycin-treated patients and 0.6, 1.0, and 1.2 mg/100 ml for the cefoxitin-treated patients. The maximal values observed were, respectively, 1.7 and 1.6 mg/100 ml in the clindamycin-treated patients and 1.4, 1.3, and

1.4 mg/100 ml in the other group. These changes were transient and disappeared after discontinuation of therapy in four patients. In one patient who received cefoxitin, the creatinine level was still 1.4 mg/100 ml at 14 days after discontinuation of therapy. In that patient, the initial creatinine level was 1.2 mg/100 ml, and the maximal rise during therapy was 1.4 mg/100 ml. One patient experienced an increase in the creatinine level while receiving gentamicin with cefoxitin. His initial creatinine level was 0.9 mg/100 ml and rose to 1.4 mg/100 ml. The creatinine level in that patient came back to pretreatment values after discontinuation of therapy.

DISCUSSION

Clindamycin is effective as a therapy of infections caused by anaerobic microorganisms (1). We have shown recently that clindamycin was effective in 70% of cases of anaerobic wound infections in cancer patients (8); a similar result was obtained with tinidazole, a derivative of metronidazole, which is specifically active against anaerobes. Clindamycin was chosen here as the reference drug to which we compared cefoxitin, a newer cephamycin which was reported to be active against anaerobes (2, 4) and in anaerobic infections (3). In our hospital, cefoxitin inhibits in vitro 73% of *B. fragilis* strains, and it is even more active against other anaerobic species. Cefoxitin also has a broad-spectrum bacterial activity against aerobic bacteria; in our center it inhibits 94% of *E. coli* isolates, 99% of *Klebsiella* sp., 99% of *Proteus* sp., and 91% of *S. aureus*.

In our small series, 78% of the patients treated with cefoxitin responded and 89% of those treated with clindamycin responded; this difference is not statistically significant. However, cefoxitin was less effective than clindamycin in eradicating the offending anaerobic pathogens from the site of infection; eradication of the pathogen was achieved in 84% of the patients who received clindamycin but in only 42% of the patients who were treated with cefoxitin. Although the number of patients was small and makes a meaningful statistical analysis unrealistic, our results suggest that there might be a relationship between the elimination of a pathogen from the site of an infection and a favorable clinical response. In addition, cefoxitin-resistant anaerobic strains were encountered more frequently than clindamycin-resistant strains. Tolerance to cefoxitin and to clindamycin was equally good and no major adverse effects were observed in this series.

Another interesting aspect of the present study relates to the investigation of the respective roles of aerobic and anaerobic microorganisms in infections from which both types of pathogens can be isolated. We suspected that aerobes were not of major importance in the infections studied here; in all cases, they were present in smaller numbers than the anaerobes, and in most cases they had not been seen on Gram-stained smears of the cultured material, although it may be impossible to distinguish between aerobic and anaerobic microorganisms on a morphological basis alone.

Aerobic microorganisms, especially gram-negative bacilli, were frequently associated with anaerobes in the present series. Among the patients who received clindamycin, all of the associated microorganisms were resistant to clindamycin; despite this, the rate of clinically favorable responses was close to 90%. Similarly, all four cefoxitin-treated patients from whom cefoxitin-resistant aerobic pathogens had been isolated in addition to anaerobes responded well to cefoxitin. These observations suggest that, in infections which appear on a clinical and a microbiological basis to be caused by anaerobes, the role of the aerobes which can be isolated at the same time might not be always clinically relevant. Another possible explanation for our results is that the aerobes need the presence of anaerobes to be fully pathogenic under certain circumstances. Further studies are required to determine whether infections caused by anaerobes mixed with aerobes require broad-spectrum antimicrobial therapy or whether a treatment aimed only at the eradication of the anaerobes might be sufficient. Our data suggest that the latter hypothesis might be correct.

It is recognized that the evaluation of therapy of complex infections, such as those superimposed on tumors or other serious underlying conditions and from which multiple possible pathogens can be isolated, is extremely difficult. Of course, the supposition that the anaerobes were the cause of infection is difficult to prove, unless a control group of patients, receiving no treatment, is studied as well. However, one might fear that such a study would not be ethically acceptable. A study examining patients with bacteremia or empyema might shed more light on the question of relative efficacy of these agents. Perhaps quantitative aerobic and anaerobic cultures would be useful to help decide what relationship the organisms have to pathogenesis. The effects of surgical drainage and debridement further complicate the investigation of the pathogenesis and treatment of this type of infection. Nevertheless, more studies should be performed to delineate the respective roles of anaerobes and aerobes in infections in which both pathogens are found at the site of infection.

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