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COMBINATION OF PIPEMIDIC ACID, COLISTIN SODIUM METHANESULFONATE AND NYSTATIN MAY BE LESS EFFECTIVE THAN NYSTATIN ALONE FOR PREVENTION OF INFECTION DURING CHEMOTHERAPY-INDUCED GRANULOCYTOPENIA IN ACUTE LEUKEMIA

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Pipemidic acid (PPA) and colistin sodium methanesulfonate (CLM) may selectively suppress aerobic gram-negative bacilli. Twenty-nine patients with acute leukemia were randomized after each course of consolidation chemotherapy to receive a single agent of nystatin (NYS) (34 courses) versus a combination of NYS, PPA and CLM (36 courses). The duration of fever over 39°C was longer with the three drug combination (4.6 ± 5.1 days) than with NYS alone (1.8 ± 1.8 days) ($P < 0.01$). Four cases of pneumonia occurred and four patients including one having pneumonia died of infection with the three drug combination, while no pneumonia or death occurred with NYS alone ($P = 0.06$ and $P = 0.06$, respectively). The combination of NYS, PPA and CLM may be less effective than NYS alone for the prevention of infection in acute leukemia patients with chemotherapy-associated granulocytopenia.

Key words: **Acute leukemia, Prevention of infection, Gut decontamination, Pipemidic acid, Colistin sodium methanesulfonate, Nystatin.**

INTRODUCTION

Despite intensive infection prevention programs, the clinical course of patients with granulocytopenia continues to be complicated by fever and infection.[1,2] The infections are most often caused by bacteria, especially aerobic gram-negative bacilli, normally dwelling in the alimentary tract;[1,3] anaerobic bacteria rarely cause infections in the immunocompromised leukemic patients. Decontamination of the alimentary tract with agents that are selectively directed against aerobic gram-negative bacilli and do not affect the anaerobic flora, therefore, may prevent infections in these patients. Several studies have shown the efficacy of trimethoprim-sulfamethoxazole, gentamicin, nalidixic acid and colistin for the prevention of infections caused by gram-negative bacilli.[4–6] We have also used polymyxin B, CLM and NYS for the same purpose (unpublished observations). Although we have evaluated the regimen as effective, the patients receiving the treatment usually had infections requiring parenteral use of antibiotics such as aminoglycoside, and cephalosporin or penicillin.

Following these observations, a study seemed necessary to evaluate the effectiveness of the drugs selectively directed against aerobic gram-negative bacilli for the prevention of infection by such microorganisms. Thus, in the present study the efficacy of a combination of NYS, PPA and CLM for the prevention of severe granulocytopenic infections was compared with that of NYS alone. The results indicated that CLM and PPA were not effective for the prevention of infection after consolidation chemotherapy despite the earlier observations that not only regimens including trimethoprim-sulfamethoxazole or gentamicin,[4,5] but a single agent of nalidixic acid or colistin[6] was effective. Use of certain antibacterial agents in granulocytopenia may sometimes have adverse effects, and could even promote infections.

Abbreviations used in this paper: PPA, pipemidic acid; CLM, colistin sodium methanesulfonate; NYS, nystatin; ara-C, cytarabine; HDARA-C, high dose ara-C; DNR, daunorubicin; DHAD, mitoxantrone; ACR, aclarubicin; ANLL, acute nonlymphocytic leukemia; ALL, acute lymphocytic leukemia; GVN, gentamicin, vancomycin and nystatin.

PATIENTS AND METHODS

Patient selection

Patients with acute leukemia in their first remission and undergoing consolidation chemotherapy between April 1985 and May 1987 at the Saitama Cancer Center Hospital were eligible for this study. A course of the consolidation chemotherapy consisted of: (1) high-dose 3.0 g m^{-2} cytarabine (ara-C) drip-infused over 3 h every 12 h for six times, (2) 45 mg m^{-2} daunorubicin (DNR) push on days 1–3 and 150–200 mg m^{-2} ara-C in continuous 24 h infusion on days 1–7, (3) 10 mg m^{-2} mitoxantrone (DHAD) push on days 1–3 and 150–200 mg m^{-2} ara-C in continuous 24 h infusion on days 1–7, or (4) 30 mg m^{-2} aclarubicin (ACR) push on days 1–5 and 100–150 mg m^{-2} ara-C in continuous 24 h infusion on days 1–7.

Infection prophylaxis

The patients were randomly assigned at the end of each course of chemotherapy prophylactically to receive NYS alone or a combination of NYS, PPA and CLM. The per oral prophylactic regimen of one NYS tablet (5×10^5 units) four times a day (regimen A), or the same dose of NYS, one PPA tablet (500 mg), and one CLM capsule (3×10^6 units) each four times a day (regimen B), was started immediately after the completion of each course of the consolidation chemotherapy, and was continued until the time the granulocyte count returned to 500 mm^{-3}. No other prophylactic measures were taken. Patients were cared for in conventional single- or four-bed rooms. At the first occurrence of fever ascribed to infection during granulocytopenia, an empiric antibiotic regimen was started.[7]

Microbiologic surveillance

After the initiation of consolidation chemotherapy, bacterial and mycologic surveillance cultures of throat, urine and stool specimens were done twice weekly for all patients. Blood samples were taken from peripheral venous sites at the first and subsequent recurrent episodes of fever exceeding 39°C, or at the change of systemic antibiotic therapies.

Evaluation and statistics

Infections were defined as *clinically documented* when signs and symptoms of infection were present but were not *microbiologically documented* with positive cultures of microorganisms from blood or the site of infection. Fever was defined as a single high temperature of more than 39°C, and was recorded as *fever of unknown origin* when no infection was documented either microbiologically or clinically. Granulocytopenia was defined as less than 500 mm^{-3} neutrophils. Patients were examined daily for mucositis, skin eruptions and other signs of infection. Nausea, vomiting and diarrhea, as side effects of antibacteriofungal regimens, were recorded daily after the chemotherapeutic course. Patients' compliance to the drugs was monitored through daily clinical rounds. Differences in proportions were analyzed for significance by the chi-square test with Yates' correction.

RESULTS

Patient characteristics

Twenty-nine patients were randomly assigned to receive one of the two prophylactic regimens after each of 70 courses of consolidation chemotherapy; nine patients were assigned once, nine patients twice, six patients three times, one patient four times, and three patients five times and one patient six times, to a prophylactic regimen for the study. Thus, 20 patients were entered in the study more than once. None of the patients had fever or infection at the time of randomization. Sixty-six of the 70 courses of treatment were for acute nonlymphocytic leukemia (ANLL), and four courses for acute lymphocytic leukemia (ALL). Granulocytopenia less than 500 mm^{-3} was achieved after all the 70 chemotherapeutic courses.

High-dose ara-C was more frequently used before NYS than before the three drug (NYS, PPA and CLM) regimen ($P < 0.01$). Patient characteristics, including age, subtype of acute leukemia and duration of less than 100 mm^{-3} granulocytopenia, were similar whether with NYS alone or with the three drug combination (Table 1).

Acquired infections

The incidences of acquired infections, temperatures more than 39°C and deaths observed during treatment with each of the two regimens are shown in Table 2. All patients developed fever except for four patients each with regimen A and regimen B, respectively, after the consolidation chemotherapy. The incidences of bacteremia, *clinically documented infections* and *fever of unknown origin* were similar

Table 1. Clinical data of patients with acute leukemia treated prophylactically for infection control

	Prophylactic regimen NYS (regimen A)	NYS + PPA + CLM (regimen B)	*P* value
No. of granulocytopenic episodes*	34	36	
Median age, yr (range)	43 (15–63)	42 (15–63)	
ANLL	31	35	
Chemotherapy regimen			
1. HDARA-C	16	7	< 0.01
2. DNR + ara-C	12	12	
3. DHAD + ara-C	3	8	
4. ACR + ara-C	3	8	
Others	0	1†	
1st or 2nd consolidation therapy	16	17	
3rd or later consolidation therapy	18	19	
Mean duration of granulocyte count < 100 mm^{-3}, days	7.0 ± 4.6	8.3 ± 4.9	
Use of amphotericin B	0	2	

*Twenty-nine patients had a total of 70 courses of consolidation chemotherapy followed by oral administration of one of the two prophylactic regimens.
†Received 1.0 mg kg^{-1} of DNR push daily for 5 days.

Table 2. Infection, fever and death in patients with acute leukemia during chemotherapy-related granulocytopenia

	Prophylactic regimen NYS (regimen A)	NYS + PPA + CLM (regimen B)	*P* value
No. of granulocytopenic episodes	34	36	
Fever	30	32	
Bacteremia	10	13	
Pneumonia	0	4	0.06
Clinically documented infection	9	9	
Fever of unknown etiology	11	10	
Mean duration of fever, days	1.8 ± 1.8	4.6 ± 5.1	< 0.01
Death	0	4	0.06

in patients with each regimen, while that of pneumonia was higher with regimen B than with regimen A ($P = 0.06$). Although almost all patients had ultimately to receive empiric treatment with systemic antibiotics because of fever during severe bone marrow aplasia, the duration of fever was significantly longer with regimen B than with regimen A ($P < 0.01$). Four patients died with regimen B; two from toxic shock due to bacteremia (accompanied by pneumonia in one), one from possible bacteremic shock without documentation of pathogens and one from cerebrovascular accident accompanied by bacteremia. No patient died with regimen A ($P = 0.06$).

Microbiologic documentation

Pathogens of bacteremia are shown in Table 3. The overall incidences of gram-negative bacilli were similar with each regimen. There were more infections caused by gram-positive cocci with regimen B than with regimen A, although the difference was not statistically significant ($P = 0.09$). *P. aeruginosa*, α-*Streptococcus*, and non-fermentative gram-negative rods (*flavobacterium* species), respectively, were detected in blood from three of the four patients who developed pneumonia. The patient who exhibited the *flavobacterium* species died of bacteremic shock in the course of his pneumonia (see above). Two of the other three patients who died during the consolidation treatment showed *P. aeruginosa* and *E. coli*, respectively, as the pathogens. None of the consolidation chemotherapy protocols were particularly related to the bacterial infections or the deaths.

Side effects and compliance

Skin rash occurred in three patients with regimen A and four with regimen B. Mild diarrhea occurred in four with regimen A and six with regimen B. Liver impairment with transient elevation of transaminase was found in one each patient with each regimen; the disease seemed more likely to have been caused by the systemic antibiotic therapy given concurrently to these patients.

Both regimens were well tolerated; only one patient with regimen A and three patients with regimen B were not compliant to the drugs. None of these patients acquired pneumonia or died during the study period.

DISCUSSION

Recent advances in chemotherapy and improvements in supportive care have made complete remission achievable in approximately 60–80% of adults with previously untreated ANLL.[8] In most chemotherapy studies, however, only 20–25% of patients who achieve complete remission remain alive and free of disease 5 years later, most treatment failure being due to leukemic recurrence.[8–10] Recently, the significance of consolidation chemotherapy has been emphasized.[9,10] However, large numbers of infection deaths are reported associated with intensive consolidation therapy in various studies.[9–11] The prevention of infection during consolidation therapy therefore seems important. In the present study, PPA and CLM were used in an attempt to prevent bacterial infections related to such therapy.

Patients with acute leukemia often have infectious complications before initial induction therapy or treatment after relapse.[4,12] This situation may complicate the evaluation of the outcome of the study. We therefore selected the consolidation to avoid difficulty in the evaluation; patients usually have no infectious complications before consolidation therapy.

Table 3. Pathogens of bacteremia in patients with acute leukemia during chemotherapy-related granulocytopenia

	Prophylactic regimen		
	NYS (regimen A)	NYS + PPA + CLM (regimen B)	*P* value
No. of granulocytopenic episodes	34	36	
Gram-negative rods, total occurrences	6	4	
P. aeruginosa	1	2	
E. coli	4	1	
Klebsiella species	1	1	
Gram-positive cocci, total occurrences	2	7	0.09
α-*Streptococcus*	2	3	
S. epidermidis	0	3	
S. aureus	0	1	
Non-fermentative gram-negative rods			
Flavobacterium	1	0	
Alcaligenes species	0	2	
Multiple	1*	0	

**K. pneumoniae* + α-*streptococcus*.

One popular regimen for the prevention of infections by microbial suppression of the alimentary tract during profound and prolonged granulocytopenia is gentamicin, vancomycin and nystatin (GVN) given orally in a liquid formation four to six times daily.[13,14] This combination has been known to suppress not only aerobic gram-negative bacilli but other organisms colonizing the alimentary canal, including the normal anaerobic flora. Certain species of the anaerobic flora constitute a natural barrier, designated 'colonization resistance', against pathogenic bacteria.[1,15,16] Since the organisms that cause infection in the granulocytopenic patient are primarily aerobic bacteria and yeast, application of the concept of colonization resistance might be of value. Drugs such as trimethoprim-sulfamethoxazole and nalidixic acid are capable of reducing the aerobic bacterial flora of the colon without suppressing the anaerobic flora. Trimethoprim-sufamethoxazole had an excellent effect on the prevention of granulocytopenic infections.[4,5] The use of this drug, however, may delay bone marrow recovery.

In the present study, PPA, an analogue of nalidixic acid, and CLM were chosen to prevent infections in addition to NYS during profound and prolonged granulocytopenia. Against our expectations, the clinical and microbiological data indicated that the combination of NYS, PPA and CLM (regimen B) was even less effective than NYS alone (regimen A) for the prevention of infections. The duration of fever over 39°C was significantly longer with the three drug combination than with NYS alone. Though not statistically significant, gram-positive cocci were detected more frequently with regimen B than with regimen A. Since neither of CLM and PPA[17] is effective against gram-positive cocci, these observations may suggest that disinfection of gram-negative bacilli by these drugs have adversely affected the normal bacterial flora in the way that gram-positive cocci could more easily propagate in the patients treated with regimen B and in whom such bacteria were documented. All infections by gram-positive cocci, most of them showing only low degrees of pathogenicity, were successfully controlled with empiric parenteral antibiotic treatment. More importantly, four pneumonias and four deaths occurred in seven patients with regimen B while none of these occurred with regimen A. Even *P. aeruginosa* and *E. coli* were detected from the patients who died or developed pneumonia being treated with regimen B. In fact, infection by gram-negative rods was documented as frequently with regimen B as with regimen A. Apparently, gram-negative pathogens were often resistant to PPA and CLM. Unfortunately, sensitivity of bacteria to PPA and CLM was not tested. Combination with NYS of other drugs which selectively suppress aerobic gram-negative bacilli more effectively than PPA or CLM, should further be attempted in future studies for the prevention of infection in granulocytopenic patients.

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