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

KAZUMI SAMPI,* MASAHARU SAKURAI,† RYOJI KUMAI,* NOBUO MASEKI,* YASUHIKO KANEKO,‡ and MASAO HATTORI*

*Hematology Clinic, and Departments of †Cancer Chemotherapy and ‡Laboratory Medicine, Saitama Cancer Center Hospital, 818 Komuro, Ina, Saitama 362, Japan

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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of infections caused by gram-negative bacilli.4-6 We have also used polymyxin B, CLM and NYS for the same purpose (unpublished observations).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 colistin6 was effective. Use of certain antibacterial agents in granulocytopenia may sometimes have adverse effects, and could even promote infections.
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 \(\times\) 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 \(\times\) 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 non-lymphocytic 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