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Granulocyte Colony-stimulating Factor (G-CSF) With or Without a Quinolone in the Prevention of Infection in Cancer Patients

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59 patients who had earlier developed an infection following antineoplastic chemotherapy were randomised to receive either granulocyte colony-stimulating factor (G-CSF) alone or G-CSF + quinolone as prophylaxis during subsequent identical chemotherapy courses. 30 patients received 48 courses of G+CSF, while 29 patients received 44 courses of G-CSF + ofloxacin or ciprofloxacin. The overall infection rate was 23%. Patients with WHO grade IV leukopenia at the onset of prophylactic treatment developed infection in 61% of cases when on G-CSF, but only in 22% when on G-CSF+quinolone ($P = 0.002$). Patients with initial leukopenia of grade WHO III–I had only a 11% infection rate showing no significant difference between the treatment groups. The median duration of leukopenia $< 1 \times 10^9$/l was 4 days for patients receiving G-CSF alone and 3.5 days for those receiving additional quinolone. Patients developing infection had grade IV leukopenia for a median of 5 days. Both prophylactic treatments were well tolerated. We conclude that when prophylactic G-CSF is initiated at WHO grade IV leukopenia, addition of an oral quinolone reduces the risk of infection.
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INTRODUCTION

INFECTION IS the immediate cause of death in many cancer patients [1, 2]. When the peripheral blood granulocyte count falls below 0.5×10^9/l, the risk of serious infection and septicaemia increases rapidly, and when granulocytopenia falls below 0.1×10^9/l, practically all patients develop life-threatening infections [3].

The suppression of potentially pathogenic micro-organisms with prophylactic antibacterial treatment could result in protection against infection [4]. Several antibiotics have been used with variable success and various adverse effects [5]. Oral ofloxacin has also been used in neutropenic cancer patients resulting in low infection rates [6]. Quinolones given alone or in combination with other antibiotics have been found to be safe and well tolerated [7–9].

Granulocyte colony-stimulating factor (G-CSF) has proven its high activity on the neutrophils, increasing the number of peripheral neutrophils and reducing risk of infection [10].

The aim of the present pilot study was to establish whether a combination of G-CSF and an antibiotic, in this case a quinolone, could further reduce the incidence of infections in cancer patients receiving antineoplastic chemotherapy.

PATIENTS AND METHODS

59 patients, 18 men and 41 women, received either G-CSF alone (30 patients/48 courses) or G-CSF plus a quinolone (29 patients/44 courses). Their mean age was 55 years, range 17–83 years. All patients had developed febrile neutropenia during their preceding chemotherapy course and were enrolled in the present study as compassionate need cases. G-CSF 0.3 mg was given as subcutaneous injection during 7–10 days. Antibiotic prophylaxis was given as ofloxacin 200 mg twice daily, orally, or

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ciprofloxacin 750 mg twice daily, orally, each concomitantly with G-CSF.

All patients had received prior antineoplastic chemotherapy: 44 for malignant lymphoma, 12 for metastatic breast cancer, 2 for Hodgkin's disease, and 1 for Sezary syndrome. 10 patients also received concomitant radiotherapy.

Blood count, neutrophil count, and lactate dehydrogenase (LDH) were performed at least before the start, during, and immediately after the end of prophylactic treatment.

Findings judged as evidence of infection were: fluctuating fever (> 38.5°C), rapid increase in C-reactive protein (CRP > 100 mg/l), or microbiological findings from foci or in two blood cultures. The infections were classified as clinically documented and microbiologically documented [11]. Patients with fever caused by the malignancy, or with fever of unknown origin were not enrolled in the present study. The patients were treated on the ward during the study.

In case of a serious infection, a combination of a β-lactam cephalosporin and a quinolone was initiated except for patients in the quinolone prophylactic group who received a β-lactam plus aminoglycoside or β-lactam plus vancomycin depending on the grade of leukopenia, presence or absence of complications (acute respiratory distress syndrome, shock), and the microbiological findings. As a rule in the Department of Radiotherapy and Oncology of Helsinki, the antibiotic treatment for severe infection is stopped after 5 days without fever, the leucocyte count increasing to safe levels, and the general condition of the patient returning to baseline. Antiviral or antifungal agents were given when considered necessary.

RESULTS

Neutrophil or leucocyte counts increased in all patients except in 2 with aplastic bone marrow demonstrated at autopsy, and in 3 patients with bone marrow involvement by malignant lymphoma. The overall infection rate was 23% (21 infection episodes during 92 courses). Both patients with aplastic bone marrow developed infection. The microbiological findings are shown in Table 1. Cultures revealed gram-positive strains in 30% of cases and gram-negative strains in 70% of cases. *Clostridium difficile* was isolated from faeces of 2 patients receiving antibiotic treatment for septicaemia.

Patients receiving only G-CSF developed infection in 31% of the courses compared to 10% in patients receiving additional quinolone ($P = 0.04$, χ^2). The difference resulted from the markedly high infection rate of patients receiving only G-CSF for severe leukopenia (Table 2). Patients with WHO grade IV leukopenia at the onset of prophylactic treatment developed infection in 61% of cases when on G-CSF, but only in 22% when on G-CSF + quinolone ($P = 0.002$, χ^2), Table 2. Patients with initial leukopenia of grade WHO III-I had only a 11% infection rate showing no significant difference between the treatment groups (Table 2).

The median duration of leukopenia < 1 × 10^9/l was 4 (range 1–∞) days for patients receiving G-CSF alone and 3.5 (range 1–7) days for those receiving additional quinolone. Patients developing infection had grade IV leukopenia for a median of 5 (range 2–∞) days. Also the median leucocyte count was lower in patients with infection (Fig. 1).

No remarkable adverse events were attributed to G-CSF or the quinolones. Mild bone pain was a complaint of 11 patients. Urticaria, probably due to G-CSF, was seen in 1 patient.

Elevated levels of LDH probably due to G-CSF were observed during 15 courses (9 with G-CSF alone and 6 with G-CSF + quinolone). The highest absolute value of LDH was 940 U/l, and LDH returned to normal during G-CSF pauses. High LDH due to the malignancy was recorded before initiation of prophylactic treatment for 29 patients.

DISCUSSION

G-CSF alone was compared with a combination of G-CSF and quinolone in prevention of infection in cancer patients receiving myelotoxic chemotherapy. The rate of infection was significantly lower in patients receiving the combination treatment.

In a previous study from our institution [6], serious infection or septicaemia developed during prophylactic ofloxacin alone in 8% of the patients if their leucocyte count was 0.6–1.0 × 10^9/l, and in 64% of patients with a leucocyte count ≤ 0.5 × 10^9/l.

In the present study, G-CSF alone results in comparable infection rates with the earlier ofloxacin group with severe leukopenia (< 0.5 × 10^9/l). Addition of a quinolone to G-CSF reduced the risk of infection in the subgroup of patients with initial leucocyte count below 1.0 × 10^9/l; their infection rates fell from 61 to 22% when quinolone was added. However, when the leucocyte count at the start of therapy is > 1.0 × 10^9/l, it

Table 1. Categories of infection and cultured microbes by treatment and initial leucocyte count

Initial leucocyte count (× 10^9/l)	Treatment					
	G-CSF alone		G-CSF + quinolone			
	C.D.	M.D.	M.D. +B.	C.D.	M.D.	M.D. +B.
≤ 0.5	2	3 *E. coli*	2 *E. coli* *Staph. epidermidis*	0	0	2 *Staph. aureus* *Staph. epidermidis*
0.6–1.0	2	1 *Staph. epidermidis*	1 *Staph. aureus*	2	0	0
1.1–2.0	1	2 *Pseudomonas* spp.	0	0	0	0
> 2.0	1	0	0	2	0	0
Total	6	6	3	4	0	2

C.D. = clinically documented; M.D. = microbiologically documented; M.D. +B. = microbiologically documented with bacteraemia.

Table 2. Results of prophylactic treatment of leukopenic cancer patients with either G-CSF alone (30 patients/48 courses) or G-CSF + quinolone (29 patients/44 courses)

	Treatment					
	G-CSF alone		G-CSF + quinolone			
Leucocyte count (× 10^9/l)	No. of courses	No. of infections (%)	No. of courses	No. of infections (%)	P (χ^2)	P (χ^2) pooled
≤ 0.5	10	7 (70%)	7	2 (29%)	0.09	0.002
0.6–1.0	8	4 (50%)	11	2 (18%)	0.14	
1.1–2.0	17	3 (18%)	17	0 (0%)	0.07	0.5
> 2.0	13	1 (8%)	9	2 (22%)	0.33	
Total	48	15 (31%)	44	6 (10%)	0.04	

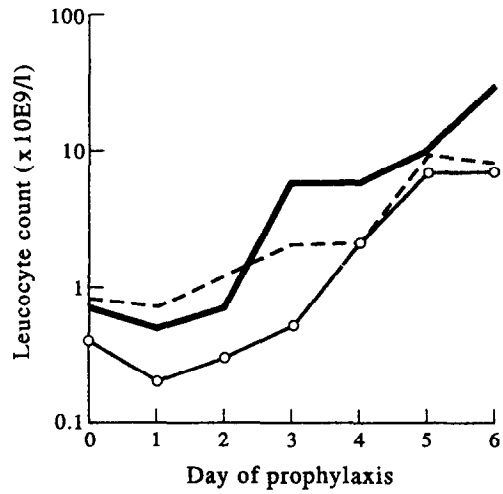

Fig. 1. Median leucocyte counts after onset of G-CSF for patients with WHO grade IV leukopenia (< 1.0 × 10^9/l). — = patients receiving G-CSF alone and not developing infection (n = 7); --- = patients receiving G-CSF + quinolone and not developing infection (n = 14); -o- = patients developing infection irrespective of prophylactic treatment (n = 15).

seems that the addition of a quinolone offers no benefit. The leucocyte recovery of patients developing infection was slower. 2 of these patients had aplastic bone marrow at autopsy. Surprisingly, no pathogens were found in cultures of these two, although the criteria of serious clinical infection were fulfilled. In febrile neutropenic patients, blood cultures were positive only in approximately 15–25% of patients with suspected septicaemia [7, 12]. This is partly due to the empirical treatment of serious infection starting immediately when criteria of serious infection are fulfilled [1, 2].

Resistance to the quinolones by *Staphylococcus epidermidis* has increased slightly in the Department of Radiotherapy and Oncology of Helsinki University, impairing further the efficacy of quinolones against this bacterium. In 1989, 45% of *Staph. epidermidis*, 24% of *Pseudomonas* sp. strains, and 3% of *Staph. aureus* showed resistance [6]. The resistance rates in 1992 are 52, 0, and 0%, respectively (unpublished data).

Quinolone adjunct did not increase the mild toxicity of prophylactic G-CSF therapy and did not add considerably to the cost and inconvenience of the treatment. According to the results of the present study, G-CSF and a quinolone should be combined when treating WHO grade IV leukopenia, but more randomised trials are needed to confirm this result.

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