Clinical impact of cycling administration of antibiotics for febrile neutropenia in Japanese patients with hematological malignancy

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Abstract

Despite the availability of newer classes of antibiotics, infection with multi-drug-resistant bacteria is a serious problem. To suppress the appearance of multi-drug-resistant bacteria and to avoid severe infection derived from febrile neutropenia (FN), we conducted cycling administration of antibiotics for FN in patients with hematological malignancy.

The treatment protocol consisted of administration of four antibiotics each for three months in one year. The above regimen was repeated for 4 years. A total of 193 patients were registered in the protocol. Mean duration of administration of cycling antibiotics was 5.9 days (range: 1-16 days). Frequency of FN before the study and during the study was unchanged until the third year but decreased significantly in the fourth year. Frequency of detection of multi-drug-resistant bacteria in the first year was the same as that before the study was started but dramatically decreased after the second year. Bacteriological treatment success rates were similar in each trimester and each year. Effective rate was not statistically different in each trimester and each year. We conclude that cycling administration of antibiotics in patients with FN is useful for suppressing the appearance of multi-drug-resistant bacteria and for obtaining excellent clinical efficacy.

Introduction

Febrile neutropenia (FN) is commonly observed in patients with hematological malignancy during chemotherapy and after hematopoietic stem cell transplantation (HSCT) and is usually rapidly progressive (1). FN must therefore be treated urgently as an infection until obtaining final results of culture. Indeed, Bodey *et al*. reported that the later the treatment was started in cases of *Pseudomonas* infection, the lower the rate of treatment success was expected to be (2). Guidelines for treatment of FN were proposed by Hughes *et al*. in 1997 and by Masaoka *et al*. in 1998 (3, 4). Thereafter, many antibiotics were reported to have a treatment success rate of 40 to 50% in FN cases with hematological malignancy (5). Guidelines for treatment of FN were revised by Hughes *et al*. in 2002 and by Tamura *et al*. in 2004 (6, 7). They recommended that patients with FN be divided into two groups (low risk and high risk groups) and treated according to the risk.

Increased quantity of administered antibiotics is usually related to appearance of and increase in antibiotic-resistant bacteria. To avoid concentrated prescription of a few antibiotics in a single institution, cycling or rotated administration of antibiotics has been recommended and performed (8). However, there are several problems to be solved: 1) basic scientific theory has not been confirmed, 2) appropriate choice of drugs, combination, and period of administration have not been established, and 3) clinical studies based on a strict protocol have not

been performed. Although Raymond *et al*. reported that more than 3 months for duration of administration resulted in increased incidence of infection (9), there are no clinical data for patients with FN.

Prophylactic administration of oral quinolones in patients with hematological diseases receiving chemotherapy and HSCT is commonly performed (10, 11, 12). Wide use of quinolones in patients with neutropenia is related to decrease in Gram-negative bacterial infection and increased incidence of Gram-positive bacterial infection (13, 14, 15). In patients with FN after autologous peripheral blood stem cell transplantation, intravenous piperacillin-tazobactam (PIPC/TAZ) as prophylaxis for FN has been reported to be more effective than fluoroquinolone (16). Meta-analysis of results of 35 studies on treatment of FN showed that cefepime (CFPM), carbapenems, cefoperazone-sulbactam (CPZ/SBT) and PIPC/TAZ were equally effective (17). Although it was also shown in that study that patients treated with CFPM are at a higher risk for fatal outcome than are patients given other beta-lactums, CFPM is widely used for FN in Japan and has been approved as treatment for FN by the Japanese Ministry of Health, Labour and Welfare. Moreover, drugs for cycling should be theoretically chosen on the basis of different mechanisms of action and different target organs of side effects. All selected antibiotics should also have an anti-Pseudomonas effect. Therefore, we conducted cycling administration of antibiotics for patients with FN who received prophylactic quinolones during chemotherapy and HSCT using CFPM, panipenem-betamipron (PAPM/BP), CPZ/SBT and PIPC/TAZ.

Materials and Methods

Study design

This was a prospective open study conducted in a single institution. The major objective of this study was to evaluate the efficacy and feasibility of cycling antibiotics for FN in patients with hematological malignancy. The primary objective was inhibition of the appearance of multi-drug-resistant bacteria and global resistance against the antibiotics used in the study. The secondary objective was comparison of the efficacy of the different antibiotics for FN. FN is defined as body temperature of more than 38.0℃for more than 1 hour, neutrophil count of less than 1,000/μL with a tendency to decrease to less than 500/μL within 24 to 48 hours or being less than 500/μL, and no basic disease to induce fever (18, 19, 20). After obtaining written informed consent, patients were treated according to the protocol. The protocol was reviewed and approved by the Institutional Review Board. The data obtained from this study were compared annually.

Treatment protocol

We conducted cycling administration of antibiotics for patients with FN who received prophylactic quinolones during chemotherapy and HSCT using CFPM (1g x 2/day), panipenem-betamipron (PAPM/BP) (1g x 2/day), CPZ/SBT (2g x 2/day) and PIPC/TAZ (2.5g x 2/day) (Table 1). These dosages were decided by

the Japanese health insurance systems. The treatment protocol consisted of administration of four antibiotics with different anti-microbial mechanisms each for three months in one year. The above regimen was repeated for 4 years. Since we conducted this study during fixed durations (three months for each drug), we did not calculate the number of subjects required to verify the goals of this study.

Patients

Adult FN patients with hematological malignancy were eligible for the study if they did not have significant hepatic or renal dysfunctions (defined as a level of bilirubin, ALT, AST, or creatinine that was less than two times the upper limit of the normal range). Dosages were not adjusted in patients whose bilirubin, ALT, AST or creatinine was less than two times the upper limit of the normal range. The patients included in this study were only patients with fever of unknown origin. Patients for whom the possibility of non-infectious fever could not be ruled out were included in this study, and patients who suffered from tumor-induced fever were excluded. Patients having a bacterial focus were also excluded from this study. Patients were excluded if they had a previous history of allergy to the antibiotics of this protocol.

Clinical and laboratory evaluations

Multi-drug-resistant bacteria are defined as oxacilin-resistant *Staphylococcus aureus* or penicillin-resistant *Streptococcus pneumoniae* and aminoglicoside,

cephem, and carbapenem-resistant Gram-negative rods. Global resistance here means resistance to the specific antibiotics cycled. In cases in which possible causal bacteria were detected by surveillance culture, bacteriological evaluation of treatment is defined as disappearance of possible causal bacteria, decrease of the bacteria, unchanged results, change of the bacteria, and unknown (21). Disappearance and decrease are defined as bacteriological treatment success.

The secondary objective was treatment success, defined as temperature being normal for at least three consecutive days without any modifications in the assigned regimen and without evidence of active infection at the time of resolution of neutropenia (20).

Adverse events were graded on the basis of the National Cancer Institute Common Toxicity Criteria version 2.0. Statistical differences were analyzed using Fisher's exact test.

Results

One hundred and ninety-three patients diagnosed as having FN were enrolled in this protocol during the period from May 2003 to April 2007 (Table 2). Twenty-three patients (12%) received autologous HSCT and 62 patients (32%) received allogeneic HSCT. Median age of the patients was 51.5 years (range: 15-79 years), and 99 (51%) of the patients were males. Underlying diseases of the patients were non-Hodgkin's lymphoma in 69 patients, acute myelogenous leukemia in 41, multiple myeloma in 16, myelodysplastic syndrome in 15, acute lymphoblastic leukemia in 13, chronic myelogenous leukemia in 8, adult T-cell leukemia in 6, Hodgkin's lymphoma in 3 and other hematological diseases in 22. Oral or intravenous administration of antibiotics was carried out in 81 patients (42%), and 69 patients (36%) received an antibiotic for decontamination of gastrointestinal tracts. Although granulocyte colony-stimulating factor (G-CSF) was used in 165 patients (85%) and macrophage colony-stimulating factor was used in 1 patient (1%), 27 patients (14%) did not receive any hematopoietic cytokines. Mean duration of administration of cycling antibiotics was 5.9 days (range: 1-16 days).

Frequency of FN before the study and during the study was unchanged until the third year but decreased significantly in the fourth year (Table 3). Clinical treatment success of cycling antibiotics in each period was statistically similar even in different years (Table 4). There was no statistical difference between the

four different antibiotics and also between different years. Although the rate of neutrophil count over 500/μl at the end of the study was slightly lower in the last year, clinical efficacy still remained high. Frequency of detection of multi-drug-resistant bacteria in colonization in the first year was the same as that before the study was started, but it decreased from the second year and was low in the third and fourth years (Table 5). Appearance of bacteria with resistance against each antibiotic used in the study did not increase compared with that before the study and remained at a low level throughout the study period. Bacteriological treatment success rates were statistically similar in the four years. There were no remarkable changes in the frequency and etiology of fungal infections during the study. Although side effects were observed in 2 to 10% of patients for every drug, grade 3 or 4 adverse effects were never observed.

Discussion

One of the most important purposes of cycling therapy is suppression of the appearance of antibiotic-resistant bacteria. In hematology, the effect of cycling therapy is easily demonstrated because of the relatively long-term administration period and frequent usage of antibiotics. This study showed that cycling of antibiotics was effective for suppressing the appearance of multi-drug-resistant bacteria from the second year and that the effect was maintained for at least three years thereafter.

The effective rates of cycling antibiotics were similar in the trimesters and in the four years. The effective rates in the present study were better than we had expected even though the subjects included 32% profound immunosuppressive patients after allogeneic HSCT. Bow *et al*. reported that CFPM and PIPC/TAZ were equally effective for treating patients with FN, about half of whom had received HSCT, and our results are compatible with their results (22). Our results also showed that the cycling protocol did not have an adverse impact on antimicrobial susceptibility compared with that before the study was started, at least in the first four years after implementation. Although quinolones are not recommended for treatment of FN because of their already wide use for prophylaxis and although we did not use quinolones in this protocol, Winston *et al*. recently reported that quinolones have an effect similar to that of carbapenems in FN (23). Therefore, cycling using quinolones should be performed in cases

without administration of prophylactic quinolones. In this study, some patients received an antibiotic for prophylaxis or decontamination of gastrointestinal tracts and others did not. Therefore, as discussed in previous reports, more studies using similar prophylactic antibiotics should be performed to determine what kinds of antibiotics are necessary, how long one treatment period should be and how long cycling the protocol should be repeated.

The degree and duration of neutropenia are among the most important factors influencing effects of antibiotics. Tamura *et al*. reported that the success rate of antibiotics in patients with FN who received the drugs when the neutrophil count was less than 500/μL was worse than that in patients who were started on antibiotics when the neutrophil count was between 500 and 1,000/μL (7). Although the rate of neutrophil count over 500/μL at the end of the study in the fourth year was significantly lower than the rates in the previous years, clinical efficacy in the fourth year was still high and similar to that in the other years. Therefore, the decrease in multi-drug-resistant bacteria after the second year might be related to maintenance of clinical efficacy of cycling antibiotics at a high level even in patients with profound neutropenia. The fact that 85% of the patients in this study had received G-CSF might have reduced the negative impact of profound neutropenia.

Bacteriological treatment success was similar in the four years. Decrease in multi-drug-resistant bacteria was not directly related to bacteriological treatment success. Hereafter, timely and efficient administration of prophylactic antibiotics

may be important. Monitoring the bacterial ecology of the units is also important for infectious control. Whether the decrease in frequency of FN in the fourth year was due to the cycling protocol used in this study should be confirmed by using another protocol with a longer treatment period.

In summary, our study clearly showed a beneficial effect of maintenance of cycling antibiotics in FN patients with hematological malignancy. Since there have been few studies providing data that show reduction in the appearance of antibiotic-resistant bacteria improves clinical outcomes and overall survival, further randomized multi-institutional studies with larger numbers of patients should be performed to determine the appropriate schedule of cycling antibiotics.

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Table 1. Cycling schedule of antibiotics

Quarter	antibiotics
May-July	cefoperazone-sulbactam (CPZ/SBT)
August-October	panipenem-betamipron (PAPM/BP)
November-January	piperacillin-tazobactam (PIPC/TAZ)
February-April	cefepime (CFPM)

Table 2. Patients' characteristics

Patient number	193
Autologous SCT	23 (12%)
Allogeneic SCT	62 (32%)
Age (years)	
Median	51.5
Range	15-79
Gender male	99 (51%)
Diagnosis	
NHL	69
AML	41
MM	16
MDS	15
ALL	13
CML	8
ATL	6
HL	3
Other	22
Administration of prophylactic antibiotics	
Oral or intravenous	81 (42%)
Decontamination of GI tracts	69 (36%)
Anti-fungal drugs	75 (39%)
Administration of cytokines	
G-CSF	165 (85%)
M-CSF	1 (1%)
None	27 (14%)
Duration of administration of cycling antibiotics (days)	
Mean	5.9
Range	1-16

Abbreviations: NHL, non-Hodgkin's lymphoma; AML, acute myelogenous leukemia: MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia;

CML, chronic myelogenous leukemia; ATL, adult T-cell leukemia; HL, Hodgkin's lymphoma; GI tracts, gastrointestinal tracts; G-CSF, granulocyte colony-stimulating factor; M-CSF, macrophage colony-stimulating factor.

Table 3. Frequency of febrile neutropenia before the study and during the study

May 2002 – April 2003	54/102* (53%)		
First year		45/101 (45%)	*NS*
Second year	55/106 (52%)	*NS*	
Third year	54/102 (53%)	*NS*	
Fourth year	39/103 (38%)	p=0.03	

*Numbers correspond to numbers of patients, not to episodes.

Table 4. Efficacy of cycling antibiotics

Quarter	effective rate	neutrophil count over 500/μl at the end of the study
May 2003-July	42%	62%
August-October	44%	33%
November-January 2004	50%	50%
February-April	56%	50%
Total	48% (19/40)	49% (22/45)
May 2004-July	71%	50%
August-October	55%	25%
November-January 2005	58%	64%
February-April	45%	46%
Total	58% (28/48) NS	47% (26/55) NS
May 2005-July	46%	50%
August-October	67%	57%
November-January 2006	42%	60%
February-April	44%	36%
Total	50% (23/46) NS	52% (28/54) NS
May 2006-July	54%	23%
August-October	43%	29%
November-January 2007	38%	11%
February-April	56%	40%
Total	49% (18/37) NS	26% (10/39) $p<0.04$

Abbreviations: NS, not significant.

Table 5. Clinical and bacteriological results

Multi-drug-resistant bacteria*				
(*MRSA, Burkholderia cepacia, Enterococcus faecium, Staphylococcus hemolytics, Pseudomonas aeruginosa*)				
2002-2003	26/54 (48%)			
First year	22/45 (49%)	NS		
Second year	11/55 (20%)	*p*=0.002		
Third year	11/54 (20%)	*p*=0.004		
Fourth year	9/39 (23%)	*p*=0.02		
Bacteria resistant against the antibiotics used in the study				
(bacteria other than multi-drug-resistant bacteria)				
	CPZ/SBT		PAPM/BP	PIPC/TAZ
	CFPM			
2003-2004	0	1	0	1
First year	1	2	0	0
Second year	1	2	2	2
Third year	1	2	0	2
Fourth year	3	0	1	1
Bacteriological treatment success				
(disappearance + decrease/detection by surveillance culture)				
First year	11/27 (41%)			
Second year	14/25 (56%)	NS		
Third year	7/17 (41%)	NS		
Fourth year	7/16 (44%)	NS		
Side effects				
Drug eruption	5 (grade 1 to 2)			
Hepatic dysfunction	4 (grade 1)			
Nausea	1 (grade 1)			
Palpitation	1 (grade 1)			
CPZ/SBT	1/56 (2%)			

PAPM/BP	2/45 (4%)
PIPC/TAZ	5/48 (10%)
CFPM	3/44 (7%)

* Multi-drug-resistant bacteria: MRSA and multi-drug-resistant Gram-negative rods showed resistance against cafazolin, cefotiam, cefmetazole, cefotaxime, ceftazidime, cefozopran, cefepime, levofloxacin, ofloxacin, gentamicin and amikacin.