# Efficacy and safety of doripenem for sepsis with neutropenia in Japanese patients with hematologic diseases

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Doripenem (DRPM) is one of the carbapenems which has a broad-spectrum and strong activity against *Pseudomonas aeruginosa*. This observational study was conducted between April 2006 and March 2007 in Japan to evaluate the efficacy and safety of DRPM 0.5 g three times a day for sepsis with neutropenia in patients with hematologic diseases. One hundred-nineteen patients were enrolled from 34 medical institutes, comprising 117 patients for safety evaluation and 104 for efficacy evaluation. Monotherapy of DRPM 0.5 g three times a day (DRPM monotherapy) was evaluated in 73 patients. The response rates of DRPM monotherapy at 72 hours and at Day 7 were 31.5% (23/73) and 67.1% (49/73), respectively. The incidence of adverse reactions including abnormal changes in laboratory values was 23.1%, and hepatic toxicity was most common. All of these adverse events were judged by the investigators as non-serious and tolerable. These results suggest that DRPM is useful for sepsis with neutropenia, though further study may be warranted.

## 1. Introduction

Doripenem (DRPM) is a carbapenem antibiotic with broad-spectrum and potent antibacterial activity against *Pseudomonas aeruginosa*[1~3]. DRPM was primarily approved in Japan in July 2005, and then in the United States in October 2007. The European Union marketing authorization for DRPM was granted in July 2008. Febrile neutropenia (FN) in association with hematologic diseases is potentially fatal. Empiric therapy with appropriate antibiotics should be instituted as soon as possible, when FN occurs. In the Infectious Diseases Society of America (IDSA) Guidelines published in 2011, monotherapy with either an antipseudomonal $\beta$-lactam or a carbapenem or piperacillin-tazobactam is recommended as the first-line empiric therapy for high risk FN patients[4]. It has been demonstrated that imipenem/cilastatin (IMP/CS), panipenem/betamipron (PAPM/BP), and meropenem (MEPM) are effective in FN[5~8]. The efficacy rate of DRPM for sepsis without neutropenia was 100% (9/9) in the clinical trial before the government approval[9]. DRPM has been expected to be effective for sepsis even with neutropenia as well. In this study, the safety and efficacy of DRPM in treatment of sepsis in neutropenic patients with hematologic diseases was evaluated.

## 2. Patients and Methods

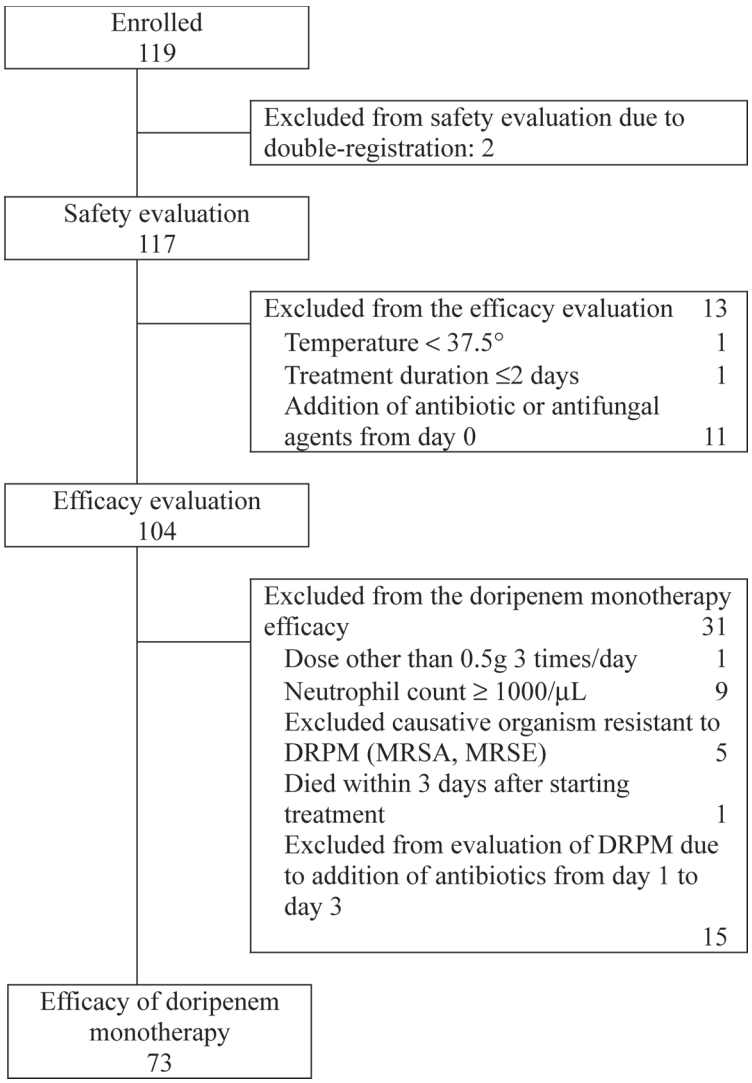
### 2.1. Subjects

Patients eligible for study inclusion were those with hematologic diseases, diagnosed with sepsis or suspicion of sepsis, treated with DRPM 0.5 g three times a day, meeting the inclusion criteria and lacking the exclusion criteria. In each institute, eligible patients were consecutively registered. Inclusion criteria were as follows: inpatients aged 16 years or older, body temperature $\geq$37.5℃ at axilla, neutrophil count either $<$500/$\mu$L or $<$1000/$\mu$L with predictable decrease to $<$500/$\mu$L. Exclusion criteria were as follows: history of shock or hypersensitivity against any of the components of DRPM, history of hypersensitivity against carbapenem, penicillin, or cephalosporin antibiotics, treatment with sodium valproate, severe hepatic or renal disorder, and infection due to causative organisms resistant to DRPM like methicillin-resistant *Staphylococcus aureus* (MRSA).

### 2.2. Study design

This study was an open-label, prospective and non-randomized clinical study. Patients were enrolled within three days after initiation of DRPM. DRPM 0.5 g was intravenously administered over 30 minutes every eight hours. The observation period was from the start of DRPM administration to seven days after completing treatment. If the duration of treatment was less than seven days, the observation period was 14 days from the start of treatment.

Fig. 1. Distribution of patients.




The following variables were collected: clinical characteristics (age, sex, weight, underlying disease, past history, history of allergy, and complications), treatment factors (prior and concomitant medications), clinical symptoms (temperature, blood pressure, pulse rate, disturbed consciousness, dyspnea), laboratory findings (urinalysis, complete blood counts, blood chemistry profiles, C-reactive protein (CRP), *β*-D-glucan, endotoxin, blood cultures), and adverse events. Severity of infection was determined according to the grade of CTCAE v3.0, as correspondence of moderate and severe to grade 3 and 4, respectively.

Response to treatment was evaluated at 72 hours and at Day 7. “Effective” in the evaluation at 72 hours was defined as follows: the daily maximum temperature dropped to less than 37.0℃ within 72 hours after the initiation of DRPM therapy (Criteria I), or fell by at least 1.0℃ to less

Table 1. Characteristics of patients in DRPM monotherapy.

| Variable | Category | N | (%) |
|---|---|---|---|
| All patients | | 73 | 100.0 |
| Sex | Male | 45 | 61.6 |
| | Female | 28 | 38.4 |
| Age (years) | Median (min-max) | 53 (17-85) | |
| Weight (kg) | Mean | 57.5 | |
| | Standard deviation | 12.0 | |
| Severity of infection | Moderate | 69 | 94.5 |
| | Severe | 4 | 5.5 |
| Duration from onset to start of treatment (days) | ≤3 | 62 | 84.9 |
| | 4-7 | 7 | 9.6 |
| | 8≤ | 4 | 5.5 |
| Underlying disease | Acute leukemia | 42 | 57.5 |
| | Malignant lymphoma | 23 | 31.5 |
| | Other [a] | 8 | 11.0 |
| Prior injectable antibiotics | No | 47 | 64.4 |
| | Yes | 26 | 35.6 |
| Prior fluoroquinolones | No | 44 | 60.3 |
| | Yes | 29 | 39.7 |
| Duration of treatment (days) | 1-3 | 2 | 2.7 |
| | 4-7 | 23 | 31.5 |
| | 8-14 | 46 | 63.0 |
| | 15≤ | 2 | 2.7 |
| | Mean | 9.3 | |
| | Standard deviation | 4.4 | |

[a] 3 myelodysplastic syndromes, 2 multiple myeloma, 1 adult T-cell lymphoma/leukemia, 1 chronic myeloid leukemia, and 1 anaplastic anemia

than 37.5℃ within 72 hours (Criteria II), and this state persisted for at least three days. “Effective” in the evaluation at Day 7 was defined as follows: the daily maximum temperature dropped to less than 37.0℃, or fell by at least 1.0℃ to less than 37.5℃ within seven days, this state persisted for at least three days, and any symptoms derived from infection were absent at Day 7. Treatment response other than the definition of “effective” was judged as “not effective”.

### 2.3. Statistical analysis

For the efficacy evaluation, the response rate was calculated as percentage of “effective” responses in the evaluation at 72 hours and at Day 7. For safety evaluation, the incidence of adverse reactions was calculated. The Clopper-Pearson method was used to calculate the confidence intervals of ratios. The $\chi^2$ test was used to compare the efficacy rates between categories of each variable, and for the purpose of this test the categories “unknown” and “missing data” were excluded. Ordinal variables were tested for trend with the Cochran-Armitage test. The presence of a linear trend in the efficacy rate in association with an increase in the category was evaluated, and the goodness of fit of the linear trend was also evaluated. For all tests, the level of significance was set at $p<0.05$, two-sided.

## 3. Results

### 3.1. Distribution and characteristics of patients

Distribution of patients is shown in Figure 1. One hundred-nineteen patients from 34 institutes in Japan were enrolled in the study. The safety and overall efficacy were evaluated in 117 and 104 patients, respectively. Thirty-one patients were excluded from the overall efficacy evaluation set, and the efficacy of DRPM monotherapy was evaluated in 73 patients, eventually. Their characteristics are shown in Table 1. All of the excluded cases violated the study protocol, thus efficacy could not be evaluated. In particular, one death case was excluded from the efficacy evaluation set of DRPM monotherapy, since the patient died of intracranial hemorrhage due to progression of acute myeloid leukemia within three days after initiation of DRPM.

### 3.2. Efficacy

#### 3.2.1. Overall response rates

The overall response rates of the 104 patients at 72 hours and at Day 7 were 27.9% (29/104) and 57.7% (60/104), respectively.

#### 3.2.2. Response rates of DRPM monotherapy

The response rates of the 73 patients with DRPM monotherapy are shown in Table 2. The response rates at 72 hours and at Day 7 were 31.5% (23/73) and 67.1% (49/73), respectively. None of the characteristics affected the response rates at 72 hours and at Day 7.

#### 3.2.3. Recurrent fever

The day of defervescence was defined as the first day when a patient was assessed as “effective” according to the efficacy criteria. Up to Day 7, fever over 37.5℃ recurred in six out of 23 cases evaluated as effective at 72 hours. These cases comprised three out of eleven and three out of twelve cases judged by Criteria I and Criteria II, respectively. The rate of recurrence was not different between these two groups ($p=0.725$).

Table 2. Response rates of DRPM monotherapy.

| Variable | Category | Response rate at 72 hours | | | Response rate at day 7 | | |
|---|---|---|---|---|---|---|---|
| | | Efficacy rate (%) | 95% CI (%) | *p*-value | Efficacy rate (%) | 95% CI (%) | *p*-value |
| All patients | | 31.5 (23/73) | (21.1, 43.4) | | 67.1 (49/73) | (55.1, 77.7) | |
| Age (years) | 16≤, <65 | 32.1 (18/56) | (20.3, 46.0) | *p*=0.8319 | 69.6 (39/56) | (55.9, 81.2) | *p*=0.4056 |
| | 65≤ | 29.4 (5/17) | (10.3, 56.0) | | 58.8 (10/17) | (32.9, 81.6) | |
| Underlying disease | Acute leukemia | 40.5 (17/42) | (0.5, 71.6) | *p*=0.4420 | 69.0 (29/42) | (28.4, 99.5) | *p*=0.1407 |
| | Malignant lymphoma | 21.7 (5/23) | (7.5, 43.7) | | 78.3 (18/23) | (56.3, 92.5) | |
| | Other | 12.5 (1/8) | (0.3, 97.5) | | 25.0 (2/8) | (3.2, 65.1) | |
| Temperature at the beginning of DRPM (°C) | 37.5≤, <38.5 | 35.1 (13/37) | (20.2, 52.5) | *p*=0.4987 | 70.3 (26/37) | (53.0, 84.1) | *p*=0.5617 |
| | 38.5≤ | 27.8 (10/36) | (14.2, 45.2) | | 63.9 (23/36) | (46.2, 79.2) | |

Table 3. Impact of prior antibiotics on response rate of DRPM monotherapy.

| Variables | Category | Efficacy rate at 72 hours | | | Efficacy rate at day 7 | | |
|---|---|---|---|---|---|---|---|
| | | Efficacy (%) | 95% CI (%) | *p*-value | Efficacy (%) | 95% CI (%) | *p*-value |
| Fluoroquinolone prophylaxis | Yes | 37.9 (11/29) | (20.7, 57.7) | *p*=0.3374 | 69.0 (20/29) | (49.2, 84.7) | *p*=0.7856 |
| | No | 27.3 (12/44) | (15.0, 42.8) | | 65.9 (29/44) | (50.1, 79.5) | |
| Prior injectable antibiotics | Yes | 30.8 (8/26) | (14.3, 51.8) | *p*=0.9196 | 61.5 (16/26) | (40.6, 79.8) | *p*=0.4500 |
| | No | 31.9 (15/47) | (19.1, 47.1) | | 70.2 (33/47) | (55.1, 82.7) | |

Table 4. Response rate by neutrophil count at 72 hours.

| neutrophil count (/μL) | | at 72 hours | | | | | Subtotals | *p*-value |
|---|---|---|---|---|---|---|---|---|
| | | <100 | 100 ≤ <500 | 500 ≤ <1000 | 1000 ≤ | Missing data | | |
| Pre-treatment | <100 | 17.6% (3/17) | 45.5% (5/11) | 50.0% (3/6) | 40.0% (4/10) | 0.0% (0/2) | 32.6% (15/46) | *p*=0.3303 |
| | 100 ≤ <500 | 33.3% (1/3) | 25.0% (2/8) | 100.0% (1/1) | 100.0% (2/2) | 25.0% (1/4) | 38.9% (7/18) | |
| | 500 ≤ <1000 | 0.0% (0/1) | 0.0% (0/1) | 50.0% (1/2) | 0.0% (0/4) | 0.0% (0/1) | 11.1% (1/9) | |
| Subtotals | | 19.0% (4/21) | 35.0% (7/20) | 55.6% (5/9) | 37.5% (6/16) | 14.3% (1/7) | 31.5% (23/73) | |
| *p*-value | | *p*=0.2531 | | | | | | |

Table 5. Response rate by neutrophil count at day 7.

| neutrophil count (/μL) | | at day 7 | | | | | Subtotals | *p*-value |
|---|---|---|---|---|---|---|---|---|
| | | <100 | 100 ≤ <500 | 500 ≤ <1000 | 1000 ≤ | Missing data | | |
| Pre-treatment | <100 | 30.0% (3/10) | 80.0% (4/5) | 100.0% (5/5) | 81.0% (17/21) | 60.0% (3/5) | 69.6% (32/46) | *p*=0.7147 |
| | 100 ≤ <500 | 100.0% (1/1) | 60.0% (3/5) | - | 75.0% (6/8) | 50.0% (2/4) | 66.7% (12/18) | |
| | 500 ≤ <1000 | 0.0% (0/1) | 100.0% (1/1) | 66.7% (2/3) | 33.3% (1/3) | 100.0% (1/1) | 55.6% (5/9) | |
| Subtotals | | 33.3% (4/12) | 72.7% (8/11) | 87.5% (7/8) | 75.0% (24/32) | 60.0% (6/10) | 67.1% (49/73) | |
| *p*-value | | *p*=0.0307 | | | | | | |

Table 6. Response rate by causative organisms.

| Causative organisms | Efficacy | |
|---|---|---|
| | at 72 hours | at day 7 |
| *Staphylococcus* spp. | 1/2 | 1/2 |
| *S. epidermidis* | 0/1 | 0/1 |
| *S. haemolyticus* | 1/1 | 1/1 |
| *Streptococcus* spp. | 2/3 | 3/3 |
| *Streptococcus* sp. | 1/1 | 1/1 |
| *S. mitis* | 1/1 | 1/1 |
| *S. intermedius* | 0/1 | 1/1 |
| *Serratia marcescens* | 0/1 | 1/1 |
| *Providencia alcalifaciens* | 0/1 | 1/1 |
| *Pseudomonas aeruginosa* | 1/4 | 2/4 |
| Totals | 4/11 | 8/11 |

**3.2.4. Impact of prior therapy on efficacy of DRPM monotherapy**

The response rates stratified by prior use of parenteral antibiotics are shown in Table 3. In all of the cases with prior antibiotics, the antibiotics were switched to DRPM because of treatment failure. The response rates at 72 hours in patients with and without prior antibiotics were 30.8% (8/26) and 31.9% (15/47) respectively, and at Day 7 were 61.5% (16/26) and 70.2% (33/47) respectively. There was no significant difference in response rates between these two groups at both of 72 hours and at Day 7.

Fluoroquinolone (FQ) prophylaxis did not influence the efficacy of DRPM at 72 hours and Day 7, as well.

**3.2.5. Impact of neutrophil count on efficacy of DRPM monotherapy**

The efficacy at 72 hours and at Day 7 stratified according to neutrophil count before and after DRPM monotherapy is shown in Tables 4 and 5. The response rates at 72 hours were not significantly different among three groups classified by the pre-treatment neutrophil count ($p=0.3303$), and among the four categories of neutrophil count at 72 hours ($p=0.2531$). In comparison with neutrophil counts before and 72 hours after DRPM initiation, there were no significant differences in the response rates among the three categories (increased, decreased, and unchanged neutrophil counts) ($p=0.1589$).

The response rates at Day 7 were not significantly different among the groups classified by the pre-treatment neutrophil count ($p=0.7147$). In contrast, there was a significant difference in the response rates among the four categories of neutrophil count at Day 7 ($p=0.0307$). In the patients with neutrophil count over 100/$\mu$L at Day 7, the response rate was significantly higher than in those with neutrophil count $<$100/$\mu$L at Day 7 ($p=0.0039$). In the patients with pre-treatment neutrophil count $<$100/$\mu$L, the increase in neutrophil count to 100/$\mu$L or more at Day 7 resulted in a significantly higher response rate ($p=0.0011$). Among the three categories (increased, decreased, and unchanged neutrophil counts), the response rate of the increasing tendency in neutrophils was significantly higher than the others ($p=0.0338$).

**3.2.6. Efficacy by causative organism of DRPM monotherapy**

Bacteria were isolated from the blood in 11 out of 73 cases. Response rate by causative organism is shown in Table 6. Overall response rates after 72 hours and Day 7 were 36% and 73%, respectively.

**3.2.7. Fatal outcomes of DRPM monotherapy**

Three deaths out of 73 cases occurred during the study period (Table 7). A 78 year-old woman with myelodysplastic syndromes died of sepsis with unknown etiology at day 4 of DRPM monotherapy. In this case, DRPM followed administration of cefepime (CFPM) for five days which failed to ameliorate sepsis, and the patient went into septic shock and multi-organ failure.

Two cases of death were caused by non-infectious complications including intracranial bleeding and an underlying disease, respectively.

Table 7. Fatal cases.

| Cause of death | Cumulative number of cases | |
|---|---|---|
| | 14 days | 30 days |
| sepsis | 1 | 1 |
| hematologic diseases | 0 | 1 |
| cerebral hemorrhage | 1 | 1 |
| total | 2 | 3 |

Table 8. Adverse reactions.

| Number of patients included in safety evaluation | | 117 | |
|---|---|---|---|
| Type of adverse drug reaction | | No. of patients | Incidence (%) |
| Abnormal changes in laboratory values | Hepatic | All hepatic function test values | 21 | 17.95 |
| | | Increased AST | 10 | 8.55 |
| | | Increased ALT | 13 | 11.11 |
| | | Increased LDH | 9 | 7.69 |
| | | Increased γ-GTP | 9 | 7.69 |
| | | Increased Al-P | 8 | 6.84 |
| | | Increased total bilirubin | 6 | 5.13 |
| | Renal | Increased BUN | 1 | 0.85 |
| | | Increased serum creatinine | 1 | 0.85 |
| | | Protein urine present | 1 | 0.85 |
| | Other | Prolonged APTT | 2 | 1.71 |
| | | Basophilia | 1 | 0.85 |
| | | Eosinophilia | 1 | 0.85 |
| | | Hyperkalemia | 1 | 0.85 |
| | | Decreased blood potassium | 1 | 0.85 |
| Symptoms | Diarrhea | | 1 | 0.85 |
| | Asthma | | 1 | 0.85 |
| | Drug eruption | | 2 | 1.71 |
| | Toxic rash | | 1 | 0.85 |
| | Total | | 27 | 23.08 |

### 3.3. Adverse reactions

The adverse reactions in 117 patients included in the safety evaluation set are listed in Table 8. Incidence of adverse reactions was 23.1% (27/117). The most common adverse reaction was

hepatic toxicity, occurring in 18.0% (21/117). There were no serious adverse reactions corresponding to Grade 3 or 4 of CTCAE v3.0, except for asymptomatic grade 3 toxicity of increased aspartate aminotransferase (AST) and hypopotassemia in two individual cases.

## 4. Discussion

Either of an antipseudomonal cephalosporin or a carbapenem or piperacillin-tazobactam is recommended for empiric therapy of FN in the practical guidelines for FN[4]. Five carbapenems including IMP/CS, MEPM, PAPM/BP, biapenem (BIPM) and DRPM are available in Japan. Prospective randomized studies on the efficacy of CFPM, MEPM and PAPM/BP against FN, which were conducted by the Japanese FN Study Group, demonstrated that overall response rates after three and seven days of treatment were about 30% and 50%, respectively, and were not different among these three agents[10,11]. The response rate of BIPM during the first seven days was reported as 67.9% in FN patients with hematopoietic diseases[12]. The present study preliminarily demonstrated that the response rates of overall patients and those with DRPM monotherapy at 72 hours and Day 7 were considered comparable to those of CFPM, MEPM and PAPM/BP, though a randomized control trial should be needed to prove non-inferiority or equality of DRPM to those agents for FN.

New evaluation criteria for efficacy were introduced in this study. The definition of significant fever is 37.5℃ or more at axillary temperature in Japan. However, traditionally defervescence has been defined as below 37.0℃. Body temperature between 37.0 and 37.5℃ was gray zone in the evaluation of efficacy. The majority of patients whose body temperature fell to between 37.0 and 37.5℃ with improvement of clinical symptoms did not need to change the first-line antibiotic therapy. In this study, the defervescence was defined as below 37.0℃ (Criteria I) or 37.5℃ with decrease over 1.0℃ (Criteria II). The determination of “with decrease over 1.0℃” was added to prevent from misjudgment of dropping down below 37.5℃ due to circadian fluctuation and measurement error as defervescence. The rate of recurrent fever in the patients evaluated as “effective” at 72 hours by Criteria II was equal to that of Criteria I. Consequently, the effectiveness assessed by Criteria II is considered as equivalent to that by Criteria I. The definition of defervescence as dropping below 37.5℃ when body temperature was decreased by at least 1℃ is reasonable in clinical practice.

The response rates at 72 hours and at Day 7 were compared between patients with and without prior parenteral antibiotics therapy. It was demonstrated that prior parenteral antibiotics did not influence these response rates, and that DRPM was effective in 61.5% of patients with prior antibiotic therapy at Day 7. The IDSA guidelines on FN recommend the shift from an initial cephalosporin to a carbapenem as well as by the addition of an aminoglycoside, ciprofloxacin, or aztreonam together with vancomycin to broaden antimicrobial coverage, when first-line empiric

therapy failed in clinically unstable FN patients without a clear source of fever[4]. Although efficacy of carbapenems in the second-line empiric therapy has not been established yet, DRPM may be considered as one of promising agents for the second-line empirical therapy in FN.

FQs are often used for prevention of bacterial infection in high-risk neutropenic patients with hematologic diseases. FQs were reported to enhance the mutation conferring carbapenem resistance in *Pseudomonas aeruginosa*, *in vitro*. Carbapenem-resistant mutants were selected in the presence of carbapenems after pre-incubation with subinhibitory concentration of a FQ (ciprofloxacin and ofloxacin). The frequency of the isolation of the mutants was higher in the selection with MEPM than DRPM, which completely inhibited growth of the mutants[13]. In the present study, the efficacies of DRPM were equivalent in patients with and without prior fluoroquinolone. DRPM is suggested to be a promising antibacterial agent for patients with FQ prophylaxis, as well.

Neutrophil counts before DRPM monotherapy had little effect on the response rates at 72 hours and Day 7. Neutrophil counts at 72 hours did not influence the response rate at 72 hours. By contrast, the response rate at Day 7 in patients with neutrophil count $<100/\mu$l at Day 7 was significantly lower than that with neutrophil count $\geq 100/\mu$l. This indicates that neutrophil count $<100/\mu$l at Day 7 is a risk factor for treatment failure. The IDSA guidelines proposed that neutrophil count $<100/\mu$l over 7 days is one of the determinants for high risk FN patients[4]. Our data, thus, agreed with the proposal of IDSA.

In this study the incidence of adverse reactions during administration of DRPM was 23.1%. The most common adverse reaction observed with DRPM was hepatic toxicity, like other carbapenems. All of adverse reactions observed with DRPM were judged to be not serious by the investigator and all were considered tolerable. These findings suggest that administration of 0.5 g three times a day of DRPM is considered as safe for the majority of Japanese patients.

In conclusion, the present study suggests that DRPM is considered to be one of the promising agents as an empiric therapy in neutropenic patients with fever and sepsis with neutropenia. Further phase 3 study is warranted to confirm the efficacy and safety of this agent.

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