J Infect Chemother 21 (2015) 654–662

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

# Efficacy and safety of tazobactam/piperacillin as an empirical treatment for the patients of adult and child with febrile neutropenia in Japan

Kazuo Tamura [a, *], Nobu Akiyama [b], Yoshinobu Kanda [c], Masahiro Saito [d]

[a] Division of Medical Oncology, Hematology and Infectious Diseases, Department of Internal Medicine, Fukuoka University Hospital, Japan
[b] Department of Hematology/Oncology, Teikyo University, School of Medicine, Japan
[c] Division of Hematology, Saitama Medical Center, Jichi Medical University, Japan
[d] Department of Pediatrics and Adolescent Medicine, Juntendo University School of Medicine, Japan

ARTICLE INFO

*Article history:*
Received 30 March 2015
Received in revised form
20 May 2015
Accepted 28 May 2015
Available online 9 June 2015

*Keywords:*
Tazobactam/piperacillin
Febrile neutropenia
Clinical trial
Pharmacokinetics

ABSTRACT

Tazobactam/piperacillin (4.5 g for adults and 90 mg/kg body weight for children, every 6 h) was administered to Japanese patients with febrile neutropenia to evaluate its defervescence and clinical efficacy and safety. The pharmacokinetics in children were also examined.

Defervescence efficacy at day 4 of the treatment was achieved in 50.0% of 94 adult and 62.5% of 8 pediatric patients, respectively. The defervescence efficacy rate in relation to the neutrophil count in adults was 37.5% for the patients with a neutrophil count of less than 100/μL and 62.5% for that between 100 and 500/μL.

The clinical efficacy rate at day 7 and at the end or discontinuation of the treatment was 79.6% and 59.1% in adult patients, respectively, and 57.1% and 75.0% in pediatric patients, respectively.

Fifteen strains of causative bacteria were isolated in 13 adult patients at baseline. All strains were eradicated within 4 days of the treatment.

The side effects that occurred in adult and pediatric patients during the treatment were all known and not specific to febrile neutropenia patients.

The pharmacokinetics profiles of tazobactam/piperacillin in children with febrile neutropenia are unlikely to be different from those in children with a common bacterial infection and without any immunosuppressive conditions. The study results in Japanese patients with febrile neutropenia demonstrate that tazobactam/piperacillin treatment is efficacious and safe in adults. As for pediatric patients, given the limited number of cases studied, further investigation is needed (Clinical trial number: Japic CTI-121728).



## 1. Introduction

Febrile neutropenia (FN) often develops following anticancer chemotherapy, hematopoietic stem cell transplantation or underlying bone marrow failure itself. Treatment with broad-spectrum antibiotics must be started immediately in such patients, as a one-day delay leads to death in more than 50% of high-risk patients. The two antibiotics available for treating FN patients in Japan are the fourth-generation cephalosporin cefepime, CFPM and the carbapenem meropenem, MEPM. These agents are among those recommended for the management of high-risk FN patients in the guidelines published by the Infectious Diseases Society of America (IDSA) [1], the National Comprehensive Cancer Network (NCCN) [2] and Japanese Society of Medical Oncology [3].

Tazobactam/piperacillin, TAZ/PIPC is a combination of the β-lactamase inhibitor tazobactam (TAZ) and the penicillin antibiotic piperacillin, PIPC at a ratio of 1:8. TAZ/PIPC provides broad-spectrum activity against gram-positive, gram-negative and anaerobic bacteria. Although TAZ/PIPC is recommended in other

* Corresponding author. Division of Medical Oncology, Hematology and Infectious Diseases, Department of Internal Medicine, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Tel.: +81 92 801 1011; fax: +81 92 801 2801.
*E-mail address:* ktamura@fukuoka-u.ac.jp (K. Tamura).

http://dx.doi.org/10.1016/j.jiac.2015.05.009
1341-321X/

countries as CFPM and MEPM, it has not been evaluated in FN patients in Japan. If its efficacy and safety are established in Japanese patients, TAZ/PIPC would provide a new treatment option and may help to control the emergence of resistant bacteria, because it possesses anti-pseudomonal activity with β-lactamase inhibition and the property of suppressing drug resistance. We investigated the efficacy and safety of TAZ/PIPC in both adult and pediatric FN patients and its pharmacokinetics in pediatric FN patients between January 2012 and August 2013.

This study was implemented in accordance with the ethical principles based on the Declaration of Helsinki, the Pharmaceutical Law, enforcement regulations of the Pharmaceutical Law, and ministerial ordinances and related notices concerning Good Clinical Practice.

## 2. Patients and methods

### 2.1. Eligibility criteria

Adults aged 16 years or older and children aged 9 months to <16 years at the time of obtaining consent were enrolled in the study. Inclusion criteria were: 1) Patients who were scheduled for or were already undergoing anticancer chemotherapy or autologous hematopoietic stem cell transplantation (HSCT) and who were predicted to develop FN. FN was defined as an axillary temperature ≥38 °C as detected by a single measurement or a fever ≥37.5 °C continuing for at least 1 h, accompanied by a neutrophil count <500/μL or 1000/μL predicted to decrease to <500/μL. 2) Subjects were required to have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels not exceeding 5-fold, and total bilirubin and serum creatinine levels not exceeding 1.5-fold of the upper limit of the institutional reference range within 7 days prior to the TAZ/PIPC treatment. 3) Adult patients were to have an estimated creatinine clearance ≥40 mL/min.

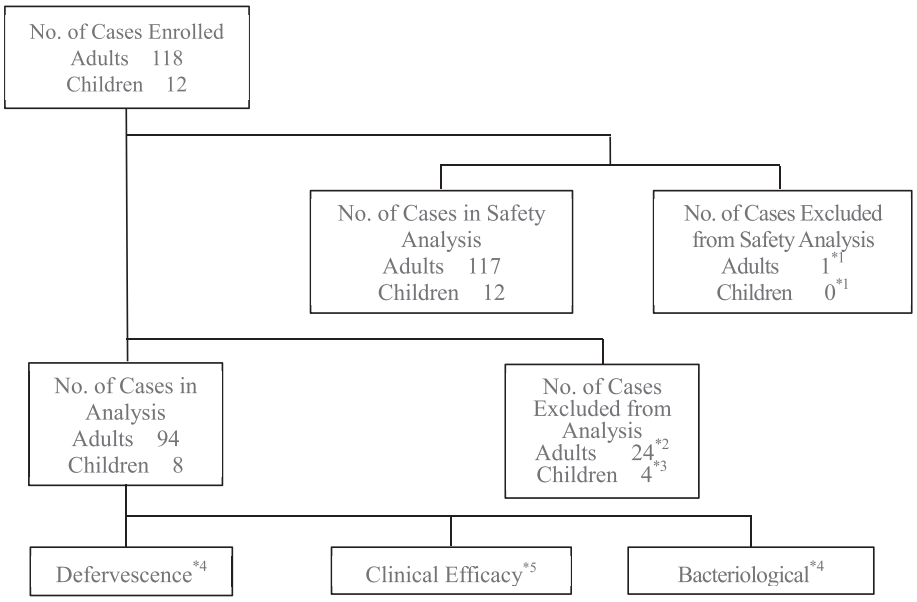
Patients who had a past history of allergy or serious side effect to the constituents of TAZ/PIPC or β-lactam antibiotics, patients who exhibited improvement in the symptoms of ongoing FN, patients who had an infection with bacterial pathogens that were not susceptible or were resistant to TAZ/PIPC, patients who were pregnant, possibly pregnant, or lactating, and patients who were regarded as ineligible by the investigator or sub-investigator were excluded from the study.

### 2.2. Antibacterial regimens

TAZ/PIPC was administered intravenously over at least 30 min at a dose of 4.5 g for adult and 90 mg/kg body weight for children, every 6 h for 7–14 days. TAZ/PIPC was continued in patients whose infection-related signs and symptoms were stable even in the absence of defervescence at day 4. Other drugs that might have affected the efficacy of TAZ/PIPC were prohibited during the trial.

### 2.3. Patient risk factors and clinical evaluation

At or before the start of the TAZ/PIPC treatment, the Multinational Association of Supportive Care in Cancer (MASCC) score was evaluated for adult patients, as were the following: the presence of a hematopoietic malignancy or solid tumor; vital signs; clinical findings such as chills and stomatitis; imaging study including chest radiography; bacteriological examinations; and serological




*1: Past history of allergy to β-lactam antibiotics

*2: Conflict with selection criteria: 4 patients; exclusion criteria: 5 patients; prohibited drug co-administration: 10 patients; prohibited drug co-administration and non-evaluable: 1 patient; and non-evaluable: 4 patients.

*3: Conflict with selection criteria and usage/dosage: 1 patient; exclusion criteria: 1 patient; usage/dosage: 1 patient; prohibited drug co-administration and non-evaluable cases: 1 patient.

*4: Evaluated on day 4, day 7 and at the end/discontinuation of the treatment.

*5: Evaluated on day 7 and at the end/discontinuation of the treatment.

**Fig. 1.** Analysis group composition.