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Original Article

Meropenem versus piperacillin/tazobactam with or without immunoglobulin as second-line therapy for febrile neutropenia in pediatric patients

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Abstract *Background:* Although survival of children with hematological diseases and cancer has increased dramatically, life-threatening complications due to bacterial infections occur in 5–10% of febrile episodes in pediatric cancer patients. A prospective randomized study was performed to clarify the usefulness of meropenem (MEPM) and piperacillin/tazobactam (PIPC/TAZ) with or without intravenous immunoglobulin (IVIG) as second-line therapy for pediatric patients with febrile neutropenia (FN).
Procedure: As first-line therapy for FN, 105 patients with 434 episodes were randomly assigned to receive MEPM or PIPC/TAZ. A total of 71 pediatric patients and 144 episodes were judged as failures and enrolled for second-line treatment. In second-line treatment, patients were randomized to a group of MEPM and PIPC/TAZ with or without IVIG. MEPM was given to patients who received PIPC/TAZ as first-line treatment, and PIPC/TAZ was given to patients who received MEPM as first-line treatment.
Results: The total success rate of second-line therapy was 49.3%. MEPM with or without IVIG was effective in 44.3% of cases, and PIPC/TAZ with or without IVIG was effective in 55.3%; this difference was not significant. The success rate in patients with serum IgG under 1000 mg/dl was 41.3% in the MEPM or PIPC/TAZ group and 64.3% in the MEPM + IVIG or PIPC/TAZ + IVIG group ($p = 0.028$).
Conclusions: The present results suggest that PIPC/TAZ is as effective as MEPM and safe for second-line treatment of FN in pediatric patients. Furthermore, IVIG appears very effective for patients with low serum IgG levels.

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Introduction

Although survival of children with hematological diseases and cancer has increased dramatically, life-threatening complications due to bacterial infections occur in 5–10% of febrile episodes in pediatric cancer patients.[1,2] In adults, piperacillin/tazobactam (PIPC/TAZ), carbapenem, and cefepime have been recommended as first-line therapy in high-risk febrile neutropenia patients.[3] However, there have been very few reports on second-line therapy for febrile neutropenia. We previously reported the efficacy of meropenem (MEPM) as second-line treatment for febrile neutropenia.[4] Furthermore, we reported the efficacy of intravenous immunoglobulin (IVIG) in patients with pediatric febrile neutropenia. Thus, a new prospective, randomized study was performed to clarify the usefulness of MEPM and PIPC/TAZ with or without IVIG as second-line therapy for pediatric patients with febrile neutropenia.

Patients and methods

From April 2012 until March 2016, febrile and neutropenic pediatric patients who had been treated with chemotherapy or had received stem cell transplantation in the pediatric unit at Sapporo Hokuyu Hospital were enrolled in this study. As first-line therapy for febrile neutropenia, 105 patients with 434 episodes were randomly assigned to receive MEPM at 120 mg/kg/day and PIPC/TAZ at 337.5 mg/kg/day. The method of sequentially numbered, opaque, sealed envelopes was used. In 47 of the 434 episodes, blood cultures before administration of the first antibiotics were positive.[5] Patients were eligible if they satisfied the following criteria: (i) fever defined as a temperature of over 37.5 °C for at least 1 h or a single temperature above 38 °C; (ii) an absolute neutrophil count (ANC) of less than 0.5×10^9/L; and (iii) no antibiotics within 72 h prior to initiation of treatment, except for trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jirovecii* pneumonia. Clinical efficacy was evaluated at 120 h, with treatment outcome criteria defined as follows. Success was defined as disappearance of fever, clinical improvement, eradication of the infecting organism, and maintenance of a response for at least 7 days after discontinuation of treatment. Failure was defined as persistence of fever or the infecting organism, any required modification of antibiotic therapy, new infections, or infection-related death. In first line therapy, 156 episodes were judged as failure (PIPC/TAZ: 85 episodes, MEPM: 71 episodes). In these episodes, 12 episodes were not treated with second line therapy. The reason was 2 dead episodes, 2 hemophagocytic syndrome, 8 use of other antibiotics according to sensitivity of pathogen. A total of 71 pediatric patients and 144 episodes were enrolled for second-line treatment. In second-line treatment, patients were randomized to a group of MEPM or PIPC/TAZ with or without IVIG at 100 mg/kg/day (maximum dose: 5 g/day) for 3 days (Venoglobulin IH 5% I.V, Japan Blood Products Organization, Tokyo, Japan). MEPM was administered at 120 mg/kg/day (maximum dose: 3 g/day) as a 1-h drip infusion 3 times a day for patients who received PIPC/TAZ as first-line treatment. On the other hand, PIPC/TAZ was administered at 337.5 mg/kg/day (maximum dose: 13.5 g/day) as a 1-h drip infusion 3 times a day for patients who received MEPM as first-line treatment (Fig. 1). This research was approved by the Institutional Review Board of our hospital. Written, informed consent was obtained from all patients or their parents. A complete history, physical examination, laboratory tests, measurements of β-D glucan and procalcitonin levels, and blood cultures were performed as clinically indicated, and a routine chest and abdominal CT scan was also performed before second-line therapy was started. When invasive fungal infection was suspected based on laboratory examinations or CT scan, anti-fungal drugs (micafungin or liposomal amphotericin) were used with the second-line therapy. Treatment was continued until completion of an appropriate course of therapy for a defined clinical or microbiological infection. The effect of second-line therapy was evaluated 72 h after the start of therapy.

Seventy-one patients with 144 febrile neutropenic episodes were enrolled in the second-line study. The patients had from 1 to 6 febrile episodes. The median age of the patients was 11.0 years (range: 0–25 years). There were 42 male and 29 female patients. Most episodes (73.6%) occurred in patients with leukemia, including acute lymphoblastic leukemia (ALL) (n = 28), acute myelogenous leukemia (AML) (n = 18), and myelodysplastic syndrome (n = 1), 1.3% of the total patients had hematological non malignancies, including aplastic anemia (n = 1) and congenital dyserythropoietic anemia (n = 1), and 25.0% of the total patients had solid tumors, including patients with hepatoblastoma (n = 3), neuroblastoma (n = 5), non-Hodgkin lymphoma (n = 7), Wilms tumor (n = 1), rhabdomyosarcoma (n = 2), EB virus-associated hemophagocytic syndrome (n = 1), malignant teratoma (n = 1), and choriocarcinoma (n = 1). In 20 episodes, the patients were registered as receiving stem cell transplantation. One patient had Down syndrome (1 episode). Intravenous antifungal drugs were administered with second-line treatment for 72 episodes including patients for whom it was used as prophylaxis at stem cell transplantation, and granulocyte colony-stimulating factor (G-CSF) was administered to 25 episodes. In 137 of the 144 episodes, a central venous catheter was used.

Statistical analysis

Differences between groups were analyzed using Fisher's exact test and the Mann–Whitney U test. Statistical analyses were performed using EZR[6] (free software).

Results

Sex, age, original disease, and the condition of the patients were not different between the MEPM and PIPC/TAZ groups (Table 1). The total success rate of second-line therapy was 49.3%. MEPM with or without IVIG was effective in 44.3% of the 79 episodes, and PIPC/TAZ with or without IVIG was effective in 55.3% of the 65 episodes; the difference was not significant. In 5 of the 144 episodes, blood cultures were positive before second-line therapy and all detected pathogens were *Staphylococcus epidermidis*, and

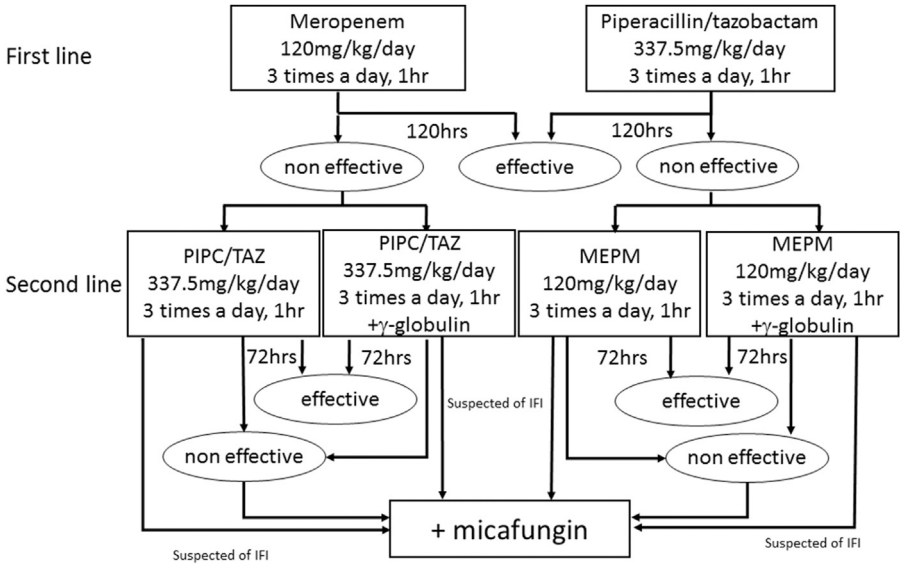

Figure 1. Study design.

Table 1 Demographic and clinical characteristics of patients with febrile neutropenia in the PIPC/TAZ and MEPM groups at the start of second-line therapy.

	PIPC/TAZ (n = 65)	MEPM(n = 79)	p
Sex (M/F)	35/30	40/39	0.739
Age, y (median, range)	12 (1–25)	11 (0–25)	0.639
Disease			0.648
ALL	28	24	
AML	20	32	
NHL	5	6	
Solid tumor	10	13	
Aplastic anemia	0	1	
Other	2	3	
Stem cell transplantation	7	13	0.347
CV line	62	75	1.000
WBC at entry ($\times 10^9$/L, median, range)	0.16 (0.01–86.60)	0.17 (0.01–23.20)	0.845
CRP at entry (mg/dl, median, range)	5.08 (0.14–27.31)	4.32 (0.14–27.95)	0.739
β-D glucan (pg/ml)	7.1 (1.2–23.1)	9.4 (1.0–144.9)	0.063
Procalcitonin (ng/ml)	0.26 (0.04–38.36)	0.28 (0.04–23.59)	0.959
IgG (mg/dl)	793 (113–2333)	847 (101–3424)	0.213

PIPC/TAZ: piperacillin/tazobactam, MEPM: meropenem, M: male, F: female, ALL: acute lymphoblastic leukemia, AML: acute myelogenous leukemia, NHL: non Hodgkin lymphoma, CV: central venous, WBC: white blood cell, CRP: C-reactive protein.

2 out of 5 episodes were effective of second line treatment. Four episodes were treated with MEPM without IVIG, and 2 episodes were effective. One episode was treated with PIPC/TAZ without IVIG and this episode was not effective. In nine patients, invasive fungal infection complicated (PIPC/TAZ without IVIG: 4, MEPM without IVIG: 2, MEPM with IVIG: 3).

A total of 81 episodes treated with MEPM or PIPC/TAZ alone and 63 episodes treated with MEPM or PIPC/TAZ with IVIG were analyzed. The characteristics of the patients in the MEPM or PIPC/TAZ and MEPM + IVIG or PIPC/TAZ + IVIG groups are shown in Table 2. Sex, age, original disease, and the condition of patients were not different between the two groups. On laboratory examinations, the WBC count and C-reactive protein, serum IgG, and procalcitonin levels were not different between the two groups. The success rates of MEPM or PIPC/TAZ treatment and MEPM + IVIG or PIPC/TAZ + IVIG treatment were 41.9% and 58.7%, respectively (p = 0.064). Success rates for episodes with absolute neutrophil counts under 0.5 $\times 10^9$/L at the end of treatment were 28.6% in the MEPM or PIPC/TAZ group and 44.7% in the MEPM + IVIG or PIPC/TAZ + IVIG group (p = 0.175). Although the success rates for episodes with serum IgG over 1000 mg/dl were 53.3% in the MEPM or PIPC/TAZ group and 47.6% in the MEPM + IVIG or PIPC/TAZ + IVIG group (p = 1.000), those in episodes with serum IgG under 1000 mg/dl were 41.3% in the MEPM or PIPC/TAZ group and 64.3% in the MEPM + IVIG or PIPC/TAZ + IVIG group (p = 0.028) (Fig. 2). Moreover, those in episodes with serum IgG under 500 mg/dl were 38.5% in the MEPM or PIPC/TAZ group and 81.8% in the MEPM + IVIG or PIPC/TAZ + IVIG group (p = 0.047). The value of serum IgG that had the highest sensitivity and specificity was 788 mg/dl on receiver operating characteristic (ROC) curve analysis. In episodes with serum IgG under 1000 mg/dl, the success rates of the MEMP + IVIG and MEPM groups were 47.8% and

Table 2 Demographic and clinical characteristics of patients with febrile neutropenia in the IVIG− and IVIG+ groups at the start of second-line therapy.

	IVIG− (n = 81)	IVIG+ (n = 63)	p
Sex (M/F)	45/36	30/33	0.402
Age, y (median, range)	12 (0−25)	12 (1−19)	0.604
Disease			0.291
ALL	35	17	
AML	27	25	
NHL	6	5	
Solid tumor	10	13	
Aplastic anemia	1	0	
Other	2	3	
Stem cell transplantation	15	5	0.089
CV line	77	60	1.000
WBC at entry ($\times 10^9$/L, median, range)	0.18 (0.01−86.60)	0.16 (0.01−22.20)	0.691
CRP at entry (mg/dl, median, range)	4.46 (0.14−27.95)	4.37 (0.18−26.72)	0.693
β-D glucan (pg/ml)	8.65 (1.0−23.1)	9.5 (1.6−144.9)	0.434
Procalcitonin (ng/ml)	0.31 (0.04−38.36)	0.26 (0.04−23.59)	0.264
IgG (mg/dl)	801 (144-2645)	858 (101-3424)	0.253

IVIG: intravenous immunoglobulin, M: male, F: female, ALL: acute lymphoblastic leukemia, AML: acute myelogenous leukemia, NHL: non Hodgkin lymphoma, CV: central venous, WBC: white blood cell, CRP: C-reactive protein.

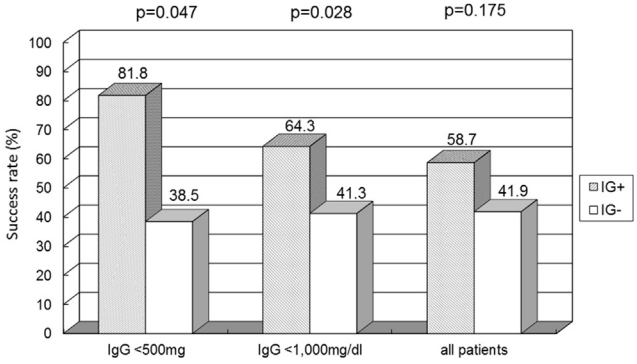

Figure 2. Success rate by the serum IgG level.

37.5%, respectively (p = 0.5807). On the other hand, those of the PIPC/TAZ + IVIG and PIPC/TAZ groups were 84.2% and 45.2%, respectively (p = 0.0080). Adverse effects were observed in 9 cases, and liver dysfunction occurred in all these cases. Three of the 9 cases were grade 2 using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, 3 cases were grade 3, and 3 were grade 4. Five of the 9 cases with liver dysfunction were in the MEPM group (3 with IVIG, 2 without IVIG), and 4 were in the PIPC/TAZ group (2 with IVIG, 2 without IVIG). One patient died from septic shock, and this patient was in the MEPM with IVIG group. However, the pathogen was not detected in this episode.

Discussion

We previously showed the efficacy of MEPM as second-line therapy for febrile neutropenia in patients with hematological diseases.[4] The efficacy of MEPM was 67.1% for the 146 episodes. Moreover, the efficacy of IVIG was also shown in that study, since the efficacy in the MEPM + IVIG group (69.4%) was superior to that in the MEPM alone group (65.5%), especially in patients with serum IgG under 500 mg/dl (81.3% vs 62.5%). However, this result was not significantly different. Since effective rate of MEPM used as second line was high, we tried to use MEPM as first-line treatment, and its efficacy was compared to PIPC/TAZ. On the other hand, use of glycopeptide antibiotic was recommended in some guideline for febrile neutropenia patients with first line failure, especially in adult patients.[3] However, we think use of a constant use of glycopeptide may promote occurrence of further resistant bacteria, because about one third to half of episodes were resistant for first line treatment. Therefore, we tried MEPM was used as second-line treatment for patients who failed PIPC/TAZ, and PIPC/TAZ was used as second-line treatment for those who failed MEPM. Moreover, we tried randomized administration of IVIG to evaluate the efficacy of IVIG for febrile neutropenia. Although we expected excellent efficacy of MEPM as first-line treatment, that of MEPM was 65.9%, superior to that PIPC/TAZ (62.4%), though this difference was not significant. In second-line treatment, the efficacy of PIPC/TAZ (55.3%) was superior to that of MEPM (44.3%), and this result was also not significantly different. The total efficacy of both groups was 77.9% in the PIPC/TAZ first and MEPM second group and 83.2% in the MEPM first and PIPC/TAZ second group (p = 0.1837). Although this result was not significantly different, first-line use of MEPM may be effective for febrile neutropenia in patients with pediatric hematological diseases. However, the efficacy of PIPC/TAZ as second-line therapy was higher than expected. The bacteria known to be resistant to MEPM and susceptible to PIPC/TAZ are *Enterococcus* spp. This bacterium was detected from only 2 patients undergoing first-line treatment. However, they may have been the origin of the fever in many patients at second line.

The exact mechanism of action of IVIG is complex and has not been fully elucidated. However, from a clinical and practical approach, it is believed that IVIG has two mechanisms of action which help in decisions regarding therapeutic intervention. As one hand, it has an immunemodulatory function that is correlated with high dose of IVIG. This includes the activation of Fc receptors causing their functional blockage and inhibiting their binding to autoimmune antibodies, modulating the production of cytokines,[7] and neutralization of circulating autoantibodies.[8–10] On the other hand, IVIG mediates a broad

spectrum of antimicrobial activity, and, therefore, can be administrated systemically to supplement the host immunity. Since antibodies facilitate antimicrobial mechanisms distinct from those of antibiotics, they do not elicit resistance and, hence, the pathogens' antibiotic resistance does not alter their bacterial susceptibility to antibody opsonization and phagocytic neutralization.[11] In vivo and in vitro, IVIG was proved to be effective for methicillin resistant *Staphylococcus aureus*.[12] Moreover, IVIG was reported to promote both the killing activity and autophagy by neutrophils of multidrug-resistant bacteria in in vitro studies.[13,14] Therefore, IVIG is widely used in replacement therapy for patients with immunodeficiency and (at doses higher than those for replacement therapy) for certain bacterial and viral infectious diseases. However, there are very few reports showing the usefulness of IVIG for bacterial infectious diseases. Masaoka et al.[15] carried out a large-scale, multicenter, randomized trial to evaluate the efficacy of IVIG in combination therapy with antibiotics for severe infection. We previously demonstrated the efficacy of IVIG especially in patients with serum IgG under 500 mg/dl.[4] In the present study, the success rate in patients given IVIG with serum IgG under 500 mg/dl was superior to that in patients who were not given IVIG, and this difference was significant. Furthermore, this result was not changed by using a cut-off value for IgG of under 1,000 mg/dl. To the best of our knowledge, this is the first report to prove the effectiveness of IVIG for pediatric patients with hematological disease. But why was IVIG more effective than in the previous study? This is a question that cannot be easily answered. However, use of MEPM, a stronger antibiotic, as first-line may be part of the answer. In patients in the second line PIPC/TAZ group who received MEPM as first-line therapy, there was a significant difference in the success rate between patients with or without IVIG. However, there was little difference between patients with or without IVIG used MEPM as second line therapy.

Given the results of the present study, one must consider whether IVIG should be used as first-line therapy with antibiotics for patients with low serum IgG levels. Since immunoglobulin is expensive and made from plasma, some may suggest that IVIG should be used carefully. However, IVIG should be used for patients with severe infections and low serum IgG levels without hesitation.

The present results suggest that PIPC/TAZ is as effective as MEPM and safe for second-line treatment of febrile episodes in neutropenic pediatric patients. Furthermore, IVIG is very effective for patients with low serum IgG levels.

Conflict of interest

All authors declare that there are no conflicts of interest to disclose.

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References

1. Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* 1997;**99**:580–8.
2. Viscoli C, Moroni C, Boni L, Bruzzi P, Comelli A, Dini G, et al. Ceftazidime plus amikacin versus ceftazidime plus vancomycin as empiric therapy in febrile neutropenic children with cancer. *Rev Infect Dis* 1991;**13**:397–404.
3. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2011;**52**:e56–93.
4. Kobayashi R, Suzuki D, Sano H, Kishimoto K, Yasuda K, Kobayashi K. Effect of meropenem with or without immunoglobulin as second-line therapy for febrile neutropenia in pediatric patients. *Pediatr Int* 2014;**56**:526–9.
5. Sano H, Kobayashi R, Suzuki D, Hori D, Kishimoto K, Kobayashi K. A prospective randomized trial comparing piperacillin/tazobactam with meropenem as empiric antibiotic treatment of febrile neutropenic children and adolescents with hematologic and malignant disorders. *Pediatric Blood & Cancer* 2017;**64**.
6. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transpl* 2013;**48**:452–8.
7. Spath PJ. Structure and function of immunoglobulin. *Sepsis* 1999;**3**:197–218.
8. Bittner D, Enk A. Intravenous immunoglobulin. In: Gaspari AA, Tyring SK, editors. *Clinical and basis immunodermatology*, vol. 3. London: Springer London; 2007. p. 605–14.
9. Ishii N, Hashimoto T, Zillikens D, Ludwig RJ. High-dose intravenous immunoglobulin (IVIG) therapy in autoimmune skin blistering diseases. *Clin Rev Allerge Immunol* 2009;**38**:186–95.
10. Peterlana D, Puccetti A, Simeoni S, Tinazzi E, Corrocher R, Lunardi C. Efficacy of intravenous immunoglobulin in chronic idiopathic pericarditis: report of four cases. *Clin Rheumatol* 2005;**24**:18–21.
11. Barekzi NA, Felts AG, Poelsta KA, Slunt JB, Grainger DW. Locally delivered polyclonal antibodies potentiate intravenous antibiotic efficacy against gram-negative infections. *Pharm Res* 2002;**19**:1801–7.
12. Farag N, Mahran L, Abou-Alsha K, El-Azizi M. Assessment of the efficacy of polyclonal intravenous immunoglobulin G (IVIG) against the infectivity of clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in vitro and in vivo. *Eur J Clin Microbiol Infect Dis* 2013;**32**:1149–60.
13. Itoh H, Matsuo H, Kitamura N, Yamamoto S, Higuchi T, Takematsu H, et al. Enhancement of neutrophil autophagy by an IVIG preparation against multidrug-resistant bacteria as well as drug-sensitive strains. *J Leukoc Biol* 2015;**98**:107–17.
14. Matsuo H, Itoh H, Kitamura N, Kamikubo Y, Higuchi T, Shiga S, et al. Intravenous immunoglobulin enhances the killing activity and autophagy of neutrophils isolated from immunocompromised patients against multidrug-resistant bacteria. *Biochem Biophys Res Commun* 2015;**14**(464):94–9.
15. Masaoka T, Hasegawa H, Takaku F, Mizoguchi H, Asano S, Ikeda Y, et al. The efficacy of intravenous immunoglobulin in combination therapy with antibiotics for severe infections. *Jpn J Chemother* 2000;**48**:199–217.