

Imipenem-Cilastatin as Initial Therapy for Febrile Cancer Patients

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Imipenem-cilastatin was used to treat 79 febrile episodes in 71 cancer patients, most of whom had neutropenia. The overall response rate was 67%, and 76% of the 45 documented infections responded. The response rates for septicemias and pneumonias were 79 and 62%, respectively. Only 1 of the 17 infections caused by gram-negative bacilli failed to respond to this therapy. The most common side effects were skin rash, nausea, and diarrhea. Eight superinfections were detected during therapy.

In the past two decades, substantial progress has been made in the management of infection in neutropenic patients. Despite advances, infection remains the major cause of morbidity and mortality in these patients. Several factors have contributed to the continuing problem of frequent infectious complications. The potential for cure of some malignancies has led to the development of intensive antitumor regimens that are associated with severe and prolonged neutropenia. The popularity of indwelling intravascular catheters has contributed to the re-emergence of gram-positive organisms as significant pathogens. The widespread use of broad-spectrum antibiotic therapy and antibiotic prophylaxis has been associated with a changing spectrum of nosocomial pathogens that are often resistant to multiple antibiotics.

The selection of antibiotic regimens for empiric therapy of fever in neutropenic patients has been going through an evolutionary process. The accepted practice for many years has been to use the combination of an aminoglycoside plus an antipseudomonal penicillin (2). The advantages of this type of regimen include broad-spectrum coverage and potential synergistic interaction against some infecting organisms. However, the disadvantages include the suboptimal efficacy of aminoglycosides in neutropenic patients, their potential for causing nephrotoxicity and audiototoxicity, and the limited activity of these combinations against many of the gram-positive organisms that have emerged as frequent pathogens.

Other approaches to empiric antibiotic therapy are under investigation. Three-drug regimens have not proved to be more effective than two-drug regimens (13, 14). The concept of combining two β -lactam antibiotics was introduced in 1969, and many studies have indicated that these regimens are as effective as a β -lactam plus an aminoglycoside (4, 8, 17, 21). The combination of an antipseudomonal penicillin plus trimethoprim-sulfamethoxazole has also been shown to be efficacious (3, 19).

The possibility of using a single antibiotic was explored first with gentamicin and subsequently with carbenicillin (5, 12). Most early studies were disappointing, primarily because of the limited activity of the antibiotics used. However, the availability of β -lactam antibiotics with a broader

spectrum of activity and the necessity of reducing hospital costs have intensified interest in this approach to the empiric therapy of febrile neutropenic patients.

Imipenem is the first of a group of carbapenem β -lactam antibiotics to be introduced for clinical investigation. Because it is degraded by a naturally occurring renal dehydropeptidase, it has been combined with cilastatin, an enzyme inhibitor with no intrinsic antibacterial activity (1). Imipenem has a broad-spectrum range of activity that includes most gram-positive cocci, gram-negative bacilli, and anaerobes (20). Clinical trials have established its efficacy and safety, but there has been minimal experience with this antibiotic in cancer patients (7). We report the results of the first open-ended trial of imipenem as initial therapy during febrile episodes in cancer patients, most of whom had neutropenia.

MATERIALS AND METHODS

Imipenem-cilastatin (hereafter referred to as imipenem) was administered as initial therapy during 91 febrile episodes in 83 cancer patients treated at The University of Texas M. D. Anderson Hospital between August and December 1984. Patients were eligible if they were neutropenic ($<1,000$ neutrophils per mm^3) and developed a temperature of $\geq 101^\circ\text{F}$ (38.3°C) that was not associated with the administration of pyrogenic substances (blood transfusions, immunotherapeutic agents, etc.). Patients who did not have clinical signs of infection or did not appear to be acutely ill were required to have persistent fever for 2 h before the institution of imipenem therapy. Patients who had recently received myelosuppressive chemotherapy and were expected to become neutropenic within 3 to 4 days were also eligible, as were patients with documented infection who were afebrile. None of these patients had received prior antibiotic therapy for this episode, although 24 patients were receiving antibiotic prophylaxis with trimethoprim-sulfamethoxazole. Patients were excluded from the study for any of the following reasons: history of anaphylactic reaction to other β -lactam compounds, severe liver or renal impairment (bilirubin >3.0 mg/dl, creatinine >3.0 mg/dl), or underlying central nervous system disease. Informed consent was obtained from all patients.

Before the start of antibiotic therapy, specimens for cultures were collected from the throat, urine, blood, sputum (if available), and any other appropriate site. When therapy was

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TABLE 1. Response by site of infection

Infection or site	No. of episodes	No. of responses (%) ^a
Septicemia	19	15 (79)
Pneumonia	13	8 (62)
Soft tissue	6	6
Head and neck	3	3
Others	4	2

^a The overall response rate was 76%.

not instituted immediately at the onset of fever, a second blood culture was obtained 2 h later, before therapy was started. A chest X ray and urinalysis were obtained within the first 12 h. Blood cultures were collected daily as long as the maximum temperature was above 101°F (38.3°C). Appropriate follow-up cultures and X-ray examinations were obtained during the course of therapy. Complete blood counts, serum electrolytes, prothrombin time, activated thromboplastin time, and an SMA 12, including blood urea nitrogen, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase, were obtained before therapy and twice weekly. The MIC of imipenem against the infecting organisms was determined by using serial twofold dilutions of the antibiotic in Mueller-Hinton broth (10).

Imipenem was used as a single antibacterial agent in a mixture containing imipenem and cilastatin in a 1:1 ratio (Merck Sharp & Dohme, Rahway, N.J.). Most patients received a dose of 1 g of imipenem dissolved in normal saline, administered intravenously over 30 to 60 min at 6-h intervals (approximately 50 mg/kg [body weight] per day). The duration of the infusion was prolonged if the patient experienced nausea or abdominal discomfort.

All patients with documented infections were treated for a minimum of 7 days or for 4 days after becoming afebrile, whichever was longer, unless untoward reactions, death, or clinical deterioration occurred. For patients with proven infections who did not respond after 3 days of imipenem therapy (as defined by continuing fever without improvement at the site of infection, increasing pulmonary infiltrates, shock, persistently positive blood cultures, etc.), the therapy was discontinued, and other appropriate antibiotics were instituted. However, if the patient had persistent neutropenia and did not respond after 48 to 72 h, leukocyte transfusions were given for 3 to 4 days if available, and imipenem was continued for an additional 3 days, after which the antibiotic therapy was changed if the patient had not responded. Therapy was altered immediately if the organism was resistant in vitro to imipenem and the patient's clinical condition rapidly worsened. Patients who received less than 12 h of antibiotic therapy were not included in this evaluation.

Episodes during which no clinical, X-ray, or bacteriologic evidence of infection was found were called fevers of unknown origin. Patients were considered to have documented infection if they had fever and clinical evidence of infection, such as cellulitis, pulmonary infiltrates, etc., although the infecting organism could not be isolated in every case. Response was defined as the disappearance of all clinical and laboratory evidence of infection when the antibiotic was discontinued. Relapse was defined as the same infection reappearing within 7 days after the discontinuation of imipenem. Patients who died of their malignant disease or of other noninfectious causes were considered to have had a response if the original infection had resolved and no evi-

dence of infection was present at postmortem examination. Superinfection was defined as infection caused by a different organism, or as infection at a different site if no organism could be isolated from the site, that occurred during treatment with imipenem or that was found at autopsy.

Statistical analyses were conducted with the Fisher exact test to determine the association between individual factors and outcome.

RESULTS

Imipenem was administered during 91 febrile episodes, but only 79 episodes occurring in 71 patients were evaluated. Twelve episodes were excluded: 6 because of protocol violations and 6 because the infections were proven to be caused by viruses or fungi. The patients included 38 males and 33 females; the median age was 44 years. Sixty-four patients had hematological malignancies; of these, 44 had acute leukemia. Two patients had lung cancer, three had sarcomas, and two had head and neck cancers. The median duration of imipenem therapy was 7 days (range, 2 to 28 days).

The overall response rate during the 79 febrile episodes was 67%. There were 34 episodes in which no infectious cause for the fever could be determined, and 19 (56%) of these responded to imipenem. Of the 45 documented infections, 76% responded. The infecting organism was identified in 28 infections, and 23 (82%) of these responded to imipenem. The response rate was 65% for the 17 infections in which the pathogen could not be isolated. This difference was statistically significant ($P = 0.05$).

Most of the documented infections were pneumonia and septicemia (Table 1). The response rate was 79% for the 19 episodes of septicemia. Six of these episodes were associated with other infections, including pneumonia ($n = 3$), urinary tract infection ($n = 2$), and perirectal infection ($n = 1$). Four of these six infections responded to imipenem therapy. Of the 13 primary septicemias, 11 responded to imipenem therapy. Twelve septicemias were caused by gram-negative bacilli, three were caused by gram-positive cocci, and four were caused by multiple organisms. The four infections that failed to respond to imipenem therapy were two polymicrobial septicemias and two *Staphylococcus aureus* septicemias, one associated with pneumonia and one associated with a urinary tract infection. In these two staphylococcal infections, blood cultures became negative, but the patients remained febrile.

The lowest response rate (62%) was observed in patients with pneumonia. The organism causing infection could be identified during only four episodes, and all four responded to imipenem therapy. Two of these pneumonias were caused by *Klebsiella pneumoniae* and one each was caused by *Streptococcus pneumoniae* and *Acinetobacter calcoaceticus*. Of the eight pneumonias in which the infecting organism could not be identified, only four responded. The other infections included one episode each of urinary tract infection and lung abscess that responded and one episode each of salpingitis and osteomyelitis that failed to respond.

The organisms causing infection were identified during 28 episodes, and 17 of these were single species of gram-negative bacilli, including *Escherichia coli* ($n = 7$), *Pseudomonas aeruginosa* ($n = 3$), *K. pneumoniae* ($n = 4$), *Serratia marcescens* ($n = 1$), and *A. calcoaceticus* ($n = 1$). The response rate was 94%; the only failure was an episode of chronic pseudomonas osteomyelitis of the mandible, in which the organism developed resistance to imipenem dur-

ing therapy. Five of the seven gram-positive coccal infections responded, including two of four caused by *S. aureus* and one each caused by *Staphylococcus epidermidis*, *S. pneumoniae*, and *Streptococcus* sp. Two of four polymicrobial infections responded: an *E. coli* and *K. pneumoniae* septicemia and an *E. coli* and α streptococcus septicemia associated with a urinary tract infection. The two failures were catheter-related *S. epidermidis* and *Propionibacterium acnes* septicemia and an *S. epidermidis* and α streptococcus septicemia.

There was no correlation between the initial neutrophil counts and response to imipenem (Table 2). Considering all patients with documented infections and those patients with severe neutropenia (<100 neutrophils per mm³), the response rate was substantially higher among the patients whose neutrophil count increased during therapy. Three neutropenic patients received leukocyte transfusions, and all responded thereafter.

All of the organisms causing infection were available for in vitro imipenem susceptibility testing. The MICs varied from ≤ 0.0125 to 3.12 $\mu\text{g/ml}$. The least susceptible organisms were four isolates of *P. aeruginosa*. The MICs of imipenem against these organisms were 1.56 to 3.12 $\mu\text{g/ml}$. The only organism that developed resistance during therapy was a *P. aeruginosa* that caused chronic osteomyelitis associated with carcinoma involving the mandible. No correlation was found between the initial MIC and the response to imipenem therapy.

The most common side effects were skin rash, nausea, and diarrhea. Six patients developed rashes, but several improved despite continuation of imipenem therapy. Twelve patients developed diarrhea; seven of them had received antitumor agents that probably contributed to this side effect. One of the remaining five patients developed hemorrhagic colitis; an assay for *Clostridium difficile* toxin was negative. One patient developed generalized seizures that recurred for 3 days during imipenem therapy and resolved with the cessation of therapy. Renal and hepatic toxicities were not observed.

Eight patients developed superinfections during therapy, but the superinfecting organism could be determined in only four of them. Two patients developed fungal superinfections, one with *Candida* septicemia and the other with *Aspergillus* pneumonia. Two patients developed bacterial superinfections: one a skin infection caused by a susceptible strain of *P. aeruginosa* (MIC, 0.78 $\mu\text{g/ml}$) and one a septicemia caused by a resistant strain of *Pseudomonas maltophilia* (MIC, >25 $\mu\text{g/ml}$). The organism causing superinfection could not be determined in two episodes of pneumonia, a dental abscess, and an enterocolitis. In an additional four patients, fever recurred although the initial infection responded, and no cause could be determined.

DISCUSSION

The customary practice has been to use an antibiotic combination as initial therapy for infection in neutropenic patients to provide broad-spectrum coverage (2). The availability of broad-spectrum β -lactam antibiotics has introduced the possibility of single-agent therapy. Several studies have compared an extended-spectrum cephalosporin with the same drug plus an aminoglycoside. Cefoperazone alone was as effective as cefoperazone plus amikacin, even in neutropenic patients (18). Ceftazidime alone was as effective as ceftazidime plus tobramycin for gram-negative bacillary

TABLE 2. Response according to neutrophil count in documented infections

Initial neutrophil count (per mm ³) and trend	No. of episodes	% Response
<100	27	74
Unchanged	18	61 ^a
Increased	9	100 ^a
100–1,000	6	83
>1,000	12	72
All infections		
Increased	22	86 ^b
Decreased or unchanged	23	65 ^b

^a $P = 0.04$.

^b $P = 0.10$.

infections but had limited activity against gram-positive infections (9). Imipenem produced an overall response rate of 67% and a response rate of 76% in documented infections, which are comparable to our results with β -lactam-plus-aminoglycoside, double β -lactam, and vancomycin-plus- β -lactam regimens (1, 8, 9; P. Jones, K. V. I. Rolston, V. Fainstein, L. Elting, R. S. Walters, and G. P. Bodey, Am. J. Med., in press).

The poorest response rates were observed in patients with fevers without evidence of infection (56%) and infections in which the pathogen could not be identified (65%). It is likely that some of the former episodes were not due to infection and that some of the latter episodes were caused by nonbacterial pathogens. Hence, the lower response rates are not surprising. The 62% response rate in pneumonia was encouraging. In most previous studies of antibiotic combinations for neutropenic patients, the response rates for pneumonia have been lower than 50% (8, 9; Jones et al., in press). The efficacy of imipenem alone against gram-negative bacterial infections was excellent, as were our previous experiences with ceftazidime and aztreonam alone (9; Jones et al., in press). Imipenem has in vitro and clinical activity against most gram-positive pathogens, but our experience was too limited to evaluate it adequately (20). The two patients with staphylococcal infections who failed to respond had negative blood cultures after imipenem therapy was initiated but remained febrile, so their therapy was changed.

The potential disadvantages with single-agent therapy are an increased risk of resistance emerging during therapy and a greater likelihood of the patient being colonized by resistant organisms. In vitro and animal studies indicate that exposure to antibiotic combinations reduces the risk of emergence of resistance (6, 15). A few clinical studies suggest that both of these events are more likely to occur during single-agent therapy, although the number of patients involved was too small to allow firm conclusions (11, 16).

Imipenem has a broad spectrum of activity and is efficacious as a single agent for initial therapy of fever in neutropenic patients. As with most antibiotics, response rates are higher among patients whose neutrophil counts recover during therapy. The drug has minimal side effects, although occasional patients have developed seizures (1). Whether single-agent therapy with imipenem will lead to increased resistance among gram-negative bacilli can be determined only after more extensive experience. Prospective randomized clinical trials comparing this antibiotic with

other regimens should further delineate its role in the cancer population.

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