

Colistin Is Effective in Treatment of Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa* in Cancer Patients[∇]

Ray Y. Hachem,^{1*} Roy F. Chemaly,¹ Corine A. Ahmar,² Ying Jiang,¹ Maha R. Boktour,¹ Georges Abou Rjaili,² Gerald P. Bodey,¹ and Issam I. Raad¹

Department of Infectious Diseases, The University of Texas M. D. Anderson Cancer Center, Houston, Texas,¹ and Staten Island University Hospital, Staten Island, New York²

Received 14 August 2006/Returned for modification 8 September 2006/Accepted 17 March 2007

The increasing incidence of infections caused by multidrug-resistant *Pseudomonas aeruginosa* is a worldwide health problem. Because no new antipseudomonal agents are expected to be available in the near future, we evaluated the safety and efficacy of colistin, an old drug with bactericidal activity against this organism. We collected clinical and demographic data on 95 cancer patients diagnosed with infections caused by multidrug-resistant *P. aeruginosa* between January 2001 and January 2004 and treated with either colistin (colistin group) or at least one active antipseudomonal agent (a beta-lactam antibiotic or a quinolone) (control group). We compared the results obtained for both groups. Thirty-one patients had been treated with colistin and 64 had been treated with an antipseudomonal non-colistin-containing regimen. Compared with the control group, patients in the colistin group had a lower median age (52 and 62 years, respectively; $P = 0.012$) but were more likely to have had nosocomial infections (87% and 64%, respectively; $P = 0.02$). Twenty-five patients (81%) in the colistin group and 40 patients (63%) in the control group had an APACHE II score of >15 ($P = 0.074$). The overall clinical response rates were 52% in the colistin group and 31% in the control group ($P = 0.055$). Multiple logistic regression analysis showed that those patients treated with colistin were 2.9 times (95% confidence interval, 1.1 to 7.6 times) more likely than those in the control group to experience a clinical response to therapy ($P = 0.026$). Colistin therapy was at least as effective and as safe a beta-lactam antibiotic or a quinolone in the treatment of infections caused by multidrug-resistant *P. aeruginosa* and, hence, may be a useful or preferred alternative therapy for this infection in cancer patients.

The increasing incidence of multidrug-resistant (MDR) *Pseudomonas aeruginosa* is a worldwide problem (2, 5, 8, 24, 33), particularly among critically ill patients, such as patients with leukemia and hematopoietic stem cell transplantation recipients. MDR *P. aeruginosa* is associated with significant morbidity and mortality (9, 21, 29); and *P. aeruginosa* infections constitute the leading cause of serious health care-associated infections and are responsible for increased lengths of hospital stay, severe illness, death, and increased cost (6). *P. aeruginosa* is the most common nosocomial organism that causes ventilator-associated pneumonia (14). Several studies have shown that ventilator-associated pneumonia due to MDR *P. aeruginosa* has a worse outcome than that due to other pathogens.

These infections are difficult to treat due to the limited therapeutic options. Colistin has excellent in vitro activity against many species of gram-negative organisms and was previously among the few agents used to treat serious infections due to *Pseudomonas* bacteremia. However, colistin use has been limited because it had limited clinical efficacy and significant nephrotoxicity and neurotoxicity (12, 13, 17, 36). Hence, it was eventually replaced by gentamicin and carbenicillin, two safer and more effective agents. However, because no new

antipseudomonal agents (31) are expected to be available in the near future, there has been growing interest in the use of colistin for the treatment of infections caused by MDR gram-negative organisms. In this study, we evaluated the efficacy and safety of intravenous colistin as therapy for MDR *P. aeruginosa* infections in a retrospective cohort study.

(A portion of this material was presented in part as an abstract at the 43rd Annual Meeting of the Infectious Diseases Society of America, San Francisco, CA, 6 to 9 October 2005.)

MATERIALS AND METHODS

Patient selection. This retrospective cohort study was performed at The University of Texas M. D. Anderson Cancer Center in Houston. After obtaining Institutional Review Board approval, we selected cancer patients with MDR *P. aeruginosa* infections from infection control surveillance records and the microbiology laboratory database. Patients had been treated in the clinic or inpatient ward during the 3-year period from January 2001 to January 2004 with intravenous colistin (colistin group) or at least one antipseudomonal agent other than colistin (a quinolone or a beta-lactam antibiotic with or without aminoglycosides to which the organism was susceptible in vitro) (control group). All patients who were included in this study were infected with a strain of *Pseudomonas* that was resistant to at least three of the five groups of antibiotics (carbapenems, quinolones, piperacillin-tazobactam or ticarcillin-clavulanic acid, cefepime or ceftazidime, and aminoglycosides). Patients were treated with colistin either because there was no other antibiotic to which the infecting organism was susceptible or the patients were failing to respond or were showing no clinical improvement to the current regimen, despite the in vitro susceptibility of the organism to the regimen.

Data collection. Clinical and demographic data were collected from the patients; their charts; and computerized administrative, pharmacy, and laboratory databases at the M. D. Anderson Cancer Center.

* Corresponding author. Mailing address: Department of Infectious Diseases, The University of Texas M. D. Anderson Cancer Center, P.O. Box 301402, Houston, TX 77230-1402. Phone: (713) 792-4389. Fax: (713) 792-8233. E-mail: rhachem@mdanderson.org.

[∇] Published ahead of print on 26 March 2007.

Dosing of colistin. Colistin (Coly-Mycin M Parenteral; Monarch Pharmaceutical, Bristol, TN) was administered intravenously at a dose of 5 mg/kg of body weight colistin base activity per day in two to four divided doses. The patients receiving hemodialysis were dosed with a 2.5-mg/kg loading dose on day 1 and then 1.5 mg/kg every 36 h of colistin base activity. The colistin dose was based on the recommendations in the package insert for anuric patients, as colistin is not effectively removed by hemodialysis. The ideal body weight was used.

Definitions. We used Centers for Disease Control and Prevention criteria to define MDR *P. aeruginosa* infection (16). An MDR *P. aeruginosa* isolate was defined as an organism that was resistant to at least three of the five antipseudomonal classes of antimicrobial agents: carbapenems, quinolones, piperacillin-tazobactam or ticarcillin-clavulanic acid, cefepime or ceftazidime, and aminoglycosides. None of the patients received a monobactam. The *Pseudomonas* isolates were identified by the classic microbiologic method. Briefly, colonies compatible with *P. aeruginosa* (gram negative, non-lactose-fermenting, oxidase-positive [usually with pyocyanin] colonies with a distinctive odor) were submitted for testing with the Vitek GNI system (product number V1316) or the API 20E system (both from BioMérieux, Marcy l'Etoile, France) for final identification. Alginate producers or unusual organisms were subjected to 16S rRNA sequencing if necessary.

Antimicrobial susceptibility testing was performed according to the guidelines of the CLSI (formerly the National Committee for Clinical Laboratory Standards), and the Etest was used (AB Biodisk, Solna, Sweden) to determine MDR (23). In particular, susceptibility to colistin was determined by the Etest agar diffusion method (AB Biodisk). The MIC was read at 24 h and was reported as a numeric MIC without interpretation. For *P. aeruginosa*, colistin MICs equal to or above the peak serum level of 4 µg/ml were considered resistance. Clinical responses below this MIC have been demonstrated for *P. aeruginosa*. These levels correspond to the manufacturer's recommendation for the investigational use of colistin and agree with recent tentative CLSI guidance for *Acinetobacter* and colistin.

The site of the infection was determined by the clinical signs and symptoms of individual patients, imaging results, and the isolation of *P. aeruginosa* from clinical specimens collected from the designated site.

Pneumonia was diagnosed as the presence of a new or progressive infiltrate, consolidation, or cavitation on chest radiographs. In addition, patients must have had a temperature of >38°C, leukopenia (leukocyte count, <4,000/mm³), or leukocytosis (leukocyte count, >12,000/mm³). Bacteremia was defined as the isolation of a *Pseudomonas* isolate from one or more blood culture specimens. Urinary tract infections (UTIs) were defined as the isolation of the organism from a urine specimen, with positive urinalysis results and signs and symptoms of UTIs. The therapy for the MDR *P. aeruginosa* infection was considered appropriate when at least one effective drug was used in the therapeutic regimen within 48 h of the development of signs of infection. The outcome of infection was assessed on day 6 as well as at the end of therapy because this has been shown in a previous study to be the mean time to the resolution of the clinical parameter (28). Monotherapy was defined as treatment with only one drug that is active against the *Pseudomonas* isolate from the regimen given to the patient. The treatment outcomes for the patients were classified as follows: (i) clinical response at day 6 and at the end of therapy, resolution of fever, leukocytosis, and local signs and symptoms of infection at day 6 as well as the end of therapy; (ii) microbiologic response, eradication of the organism that caused the infection, as evidenced by repeated negative culture at the end of therapy; (iii) failure, the absence of a resolution or the worsening of the signs and symptoms of infection; and (iv) relapse, a recurrence of the infection with the same organism at any body site within a month after the discontinuation of therapy.

Neutropenia was defined as an absolute neutrophil count of ≤500 cells/mm³. Nephrotoxicity was defined as an increase in the serum creatinine level of 50% or by 1 mg/dl with respect to the baseline level during therapy. The baseline and the final serum creatinine values were evaluated as the levels before the initiation of therapy and within 2 days after the administration of the last dose of therapy.

Statistical analysis. Chi-square or Fisher's exact test was used to compare categorical variables, as appropriate. Continuous variables were compared by Wilcoxon rank sum tests due to the significant deviation of the data from the normal distribution. All tests were two sided, and statistical significance was set at a *P* value of ≤0.05.

In addition to the general analyses, subset analyses were performed for different subgroups by comparing the outcomes between the colistin patients and the control patients.

Furthermore, logistic regression was used to determine the adjusted effect of therapy on each of the three outcomes: clinical response, microbiologic response, and infection-related death. The factors that we evaluated included age, underlying disease, stay in an intensive care unit (ICU) during infection,

APACHE II score, hemodialysis within 30 days prior to a positive culture, neutropenia (defined as an absolute neutrophil count of <500 cells/mm³) during infection, hospital admission within 30 days prior to infection, nosocomial infection, whether the organisms were resistant to the antibiotics in the five antibiotic groups, whether the patient had bacteremia or pneumonia, and the number of antibiotic groups used for therapy. First, univariate analyses were performed to evaluate the predictive effect of each factor alone. Then, in addition to treatment, any factor whose univariate test result had a *P* value of <0.25 was included in a full multiple logistic model. Finally, the full model was reduced one factor at a time such that all factors remaining in the model were statistically significant at a 5% significance level, except that treatment remained in the model, regardless of its *P* value. Similar logistic analyses were also performed for the monotherapy subgroup, when appropriate. All the statistical analyses were performed by using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

We identified 95 patients infected with MDR *P. aeruginosa* during the study period: 31 had been treated with a colistin-containing regimen and 64 had been treated with other antipseudomonal agents. Most patients were male (colistin group, 71%; control group, 62%) (Table 1). The median age of the control group (62 years; age range, 3 to 82 years) was significantly higher than that of the colistin group (52 years; age range, 10 to 72 years) (*P* = 0.012).

The type of underlying malignancy was significantly different between the colistin group (leukemia, 64%; lymphoma/myeloma, 13%; and solid tumor, 23%) and the control group (leukemia, 38%; lymphoma/myeloma, 14%; and solid tumor, 48%) (*P* = 0.033). The median APACHE II score was similar for both groups (17 for the colistin group and 16 for the control group; *P* = 0.38). The colistin-treated patients were more likely than the control patients to have had a hospital admission within 30 days of the first positive culture (97% and 61%, respectively; *P* = 0.0002) and more likely to have had a nosocomial infection (87% and 64%, respectively; *P* = 0.02). Furthermore, the patients in the colistin group were more likely than those in the control group to have harbored a *Pseudomonas* strain with aminoglycoside resistance (61% and 34%, respectively; *P* = 0.013) and with antipseudomonal penicillin resistance (74% and 52%, respectively; *P* = 0.036). In the overall population there was no difference between the colistin group and the control group with respect to treatment with a quinolone, cephalosporin, or penicillin. However, carbapenems and aminoglycosides were more commonly used in the control group than in the colistin group (72% and 35%, respectively, for carbapenems [*P* = 0.007] and 67% and 42%, respectively, for aminoglycosides [*P* = 0.019]).

Univariate and multiple logistic regression analyses for outcomes. In the univariate analysis, no outcome variables at day 6 and the end of the therapy, including clinical response, microbiologic response, and infection-related mortality, were significantly different between the colistin and control groups, although there was a trend for a clinical response in favor of the colistin group (Table 2). Among the 13 patients who received colistin with other drugs, 5 had a clinical response. Of those, three received an active agent, while the other two received no active alternative antipseudomonal agents (Table 3). The nephrotoxicity rates were similar for both groups: 7 (23%) in the colistin group and 14 (22%) in the control group (*P* = 0.94). However, the multiple logistic regression analysis

TABLE 1. Demographic and clinical characteristics of patients in colistin and control groups

| Characteristic | Colistin group (n = 31) | Control group (n = 64) | P value |
|---------------------------------------------------------------------------------|-------------------------|------------------------|---------|
| Median (range) age (yr) | 52 (10–72) | 62 (3–82) | 0.012 |
| Sex (no. [%] of patients) | | | |
| Male | 22 (71) | 40 (62) | 0.42 |
| Female | 9 (29) | 24 (38) | |
| Underlying disease (no. [%] of patients) | | | 0.033 |
| Leukemia | 20 (64) | 24 (38) | |
| Lymphoma/myeloma | 4 (13) | 9 (14) | |
| Solid tumor | 7 (23) | 31 (48) | |
| ICU stay (no. [%] of patients): | | | |
| Within 30 days prior to infection | 17 (55) | 30 (47) | 0.47 |
| During infection | 21 (68) | 37 (58) | 0.35 |
| Median (range) APACHE II score | 17 (11–27) | 16 (7–32) | 0.38 |
| No. (%) of patients with: | | | |
| Mechanical ventilation within prior mo | 15 (48) | 28 (44) | 0.67 |
| Hemodialysis within prior mo | 8 (26) | 8 (12) | 0.10 |
| Neutropenia within 30 days prior to infection | 17 (55) | 30 (47) | 0.47 |
| Median (range) duration (days) of neutropenia within 30 days prior to infection | (3–31) | (1–122) | 0.89 |
| Neutropenia during infection (no. [%] of patients) | 14 (45) | 24 (37) | 0.48 |
| Median (range) duration (days) of neutropenia during infection | (2–118) | (2–100) | 0.32 |
| No. (%) of patients with: | | | |
| <i>Pseudomonas</i> infection or colonization (within prior year) | 13 (42) | 31 (48) | 0.55 |
| Polymicrobial infection | 16 (52) | 30 (47) | 0.67 |
| Hospital admission within 30 days prior to infection | 30 (97) | 39 (61) | 0.0002 |
| Nosocomial infection | 27 (87) | 41 (64) | 0.02 |
| Antibiotic resistance | | | |
| Three classes | 7 (23) | 18 (28) | 0.57 |
| Four classes | 7 (23) | 26 (41) | 0.083 |
| Five classes | 16 (52) | 10 (16) | 0.0002 |
| Bacteremia | 14 (45) | 22 (34) | 0.31 |
| Pneumonia | 17 (55) | 30 (47) | 0.47 |
| UTI | 0 | 7 (11) | 0.056 |
| Wound | 0 | 5 (8) | 0.17 |
| Median (range) treatment duration (days) | 20 (5–58) | 20 (3–120) | 0.53 |

TABLE 2. Overall outcomes and toxicity in colistin and control groups

| Outcome | No. (%) of patients | | P value |
|-----------------------------|-------------------------|------------------------|---------|
| | Colistin group (n = 31) | Control group (n = 64) | |
| Nephrotoxicity | 7 (23) | 14 (22) | 0.94 |
| Clinical response at: | | | |
| Day 6 | 16 (52) | 20 (31) | 0.055 |
| End of therapy | 16 (52) | 22 (34) | 0.11 |
| Microbiologic response at: | | | |
| Day 6 | 15 (48) | 25 (39) | 0.39 |
| End of therapy | 15 (48) | 26 (41) | 0.47 |
| Relapse | 3 (10) | 7 (11) | >0.99 |
| Infection-related mortality | 8 (26) | 11 (17) | 0.33 |
| Overall mortality | 19 (61) | 30 (47) | 0.19 |

indicated a significantly higher clinical response rate in patients who received colistin (odds ratio [OR], 2.9; 95% confidence interval [CI], 1.1 to 7.6; $P = 0.026$) but no difference in the microbiologic response rate (OR, 1.7; 95% CI, 0.7 to 4.3; $P = 0.24$) (Table 4). In the cohort of 95 patients there were 19 infection-related deaths (20%). According to a chi-square test, there was no significant difference in the infection-related mortality rate between the two treatment groups (26% for the colistin group and 17% for the control group; $P = 0.33$). The two predictors of infection-related death were an underlying diagnosis of leukemia (OR, 5.0; 95% CI, 1.3 to 19.4; $P = 0.019$) or lymphoma/multiple myeloma (OR, 11.3; 95% CI, 1.7 to 72.7; $P = 0.019$) and ICU stay (OR, 14.2; 95% CI, 2.7 to 74.7; $P = 0.0018$).

Patients in ICU at the time of infection. The critically ill patient subgroup analysis contained 21 patients in the colistin group and 37 patients in the control group. These two treatment groups were not significantly different with respect to any of the outcome variables (data not shown).

TABLE 3. Analysis of clinical response by antibiotic class among patients who received colistin with other drugs ($n = 13$)

| Antibiotic used along with colistin | No. of patients | No. (%) of patients with a clinical response |
|-------------------------------------|-----------------|----------------------------------------------|
| Aminoglycosides | 8 | 2 (25) |
| Active | 6 | 1 (17) |
| Nonactive | 2 | 1 (50) |
| Carbapenems | 4 | 1 (25) |
| Active | 1 | 1 (100) |
| Nonactive | 3 | 0 (0) |
| Cephalosporins | 7 | 2 (29) |
| Active | | |
| Nonactive | 7 | 2 (29) |
| Fluoroquinolones | 8 | 1 (13) |
| Active | | |
| Nonactive | 8 | 1 (13) |
| Penicillins (antipseudomonal) | 8 | 2 (25) |
| Active | 6 | 2 (33) |
| Nonactive | 2 | 0 (0) |

Patients with neutropenia at the time of infection. The “neutropenic onset of infection” subgroup analysis contained 14 patients in the colistin group and 24 patients in the control group. The two treatment groups were not significantly differ-

TABLE 4. Multiple logistic regression models for outcomes ($n = 95$)

| Outcome and variable | No. of patients | OR (95% CI) | P value |
|--------------------------------|-----------------|------------------|-----------|
| Clinical response | | | |
| ICU stay during infection | | | 0.0054 |
| No | 37 | 3.7 (1.5, 9.2) | |
| Yes | 58 | 1.0 | |
| Treatment | | | 0.026 |
| Colistin | 31 | 2.9 (1.1, 7.6) | |
| Control | 64 | 1.0 | |
| Microbial response | | | |
| ICU stay during infection | | | 0.0053 |
| No | 37 | 3.5 (1.5, 8.4) | |
| Yes | 58 | 1.0 | |
| Treatment | | | 0.24 |
| Colistin | 31 | 1.7 (0.7, 4.3) | |
| Control | 64 | 1.0 | |
| Infection-related death | | | |
| Underlying disease | | | 0.019 |
| Leukemia | 44 | 5.0 (1.3, 19.4) | |
| Lymphoma/myeloma | 13 | 11.3 (1.7, 72.7) | |
| Solid tumor | 38 | 1.0 | |
| ICU stay during infection | | | 0.0018 |
| Yes | 58 | 14.2 (2.7, 74.7) | |
| No | 37 | 1.0 | |
| Treatment | | | 0.92 |
| Colistin | 31 | 1.1 (0.3, 3.5) | |
| Control | 64 | 1.0 | |

TABLE 5. Outcomes for patients receiving monotherapy for *Pseudomonas aeruginosa* infection

| Outcome | No. (%) of patients | | P value |
|-----------------------------|-----------------------------|----------------------------|-----------|
| | Colistin group ($n = 18$) | Control group ($n = 35$) | |
| Nephrotoxicity | 4 (22) | 5 (14) | 0.47 |
| Clinical response at: | | | |
| Day 6 | 11 (61) | 9 (26) | 0.012 |
| End of therapy | 11 (61) | 11 (31) | 0.038 |
| Microbiologic response at: | | | |
| Day 6 | 11 (61) | 12 (34) | 0.062 |
| End of therapy | 11 (61) | 13 (37) | 0.097 |
| Relapse | 0 | 2 (6) | 0.54 |
| Infection-related mortality | 4 (22) | 9 (26) | >0.99 |
| Overall mortality | 12 (67) | 16 (46) | 0.15 |

ent with respect to any of the outcome variables or toxicity (data not shown).

Patients with bacteremia and patients with pneumonia. Similarly, subgroup analyses showed no difference in any of the outcome variables between the two groups of patients with bacteremia and patients with pneumonia (data not shown), although it showed a trend for the colistin group to have a higher clinical response rate than the control group for pneumonia patients (47% and 20%, respectively; $P = 0.09$).

Monotherapy subgroup analyses. The monotherapy subgroup included 18 patients treated with colistin and 35 patients treated with a single antipseudomonal agent for MDR *P. aeruginosa*. Of the patients who received monotherapy, those in the colistin group were more likely than those in the control group to experience a clinical response at day 6 (61% and 26%, respectively; $P = 0.012$) and with a similar trend for microbiologic response (61% and 34%, respectively; $P = 0.062$) (Table 5). Finally, multiple logistic regression analyses showed that among the patients who were receiving monotherapy for *Pseudomonas* infection, the colistin group had higher clinical responses (OR, 11.3; 95% CI, 2.1 to 61.0; $P = 0.0048$) and microbiologic responses (OR, 6.7; 95% CI, 1.5 to 30.4; $P = 0.013$) than the control group (Table 6).

DISCUSSION

An important finding in our study was that patients who received colistin therapy had greater clinical responses at day 6 than the control group, although the rate of infection-related mortality was not significantly different between the two groups. Furthermore, colistin-treated patients who harbored an MDR *P. aeruginosa* isolate resistant to all available antipseudomonal drugs had higher clinical and microbiologic responses than the control group patients who harbored an MDR *P. aeruginosa* isolate susceptible to only one antipseudomonal drug. We did not encounter a higher incidence of nephrotoxicity in the colistin group. The incidence of nephrotoxicity observed in our study is consistent with the results reported in other studies (15, 19, 20). All of these findings

TABLE 6. Multiple logistic regression models for outcomes for patients receiving monotherapy for *Pseudomonas aeruginosa* infection (n = 53)

| Outcome and variable | No. of patients | OR (95% CI) | P value |
|-------------------------------|-----------------|------------------|---------|
| Clinical response | | | |
| ICU stay during infection | | | 0.0042 |
| No | 20 | 11.4 (2.2, 59.8) | |
| Yes | 33 | 1.0 | |
| Treatment | | | 0.0048 |
| Colistin | 18 | 11.3 (2.1, 61.0) | |
| Control | 35 | 1.0 | |
| Microbial response | | | |
| ICU stay during infection | | | 0.0032 |
| No | 20 | 10.2 (2.2, 47.9) | |
| Yes | 33 | 1.0 | |
| No. of antibiotic groups used | | | 0.019 |
| Three or less | 41 | 11.9 (1.5, 95.4) | |
| More than three | 12 | 1.0 | |
| Treatment | | | 0.013 |
| Colistin | 18 | 6.7 (1.5, 30.4) | |
| Control | 35 | 1.0 | |

suggest that colistin may be an alternative therapy for cancer patients with MDR *P. aeruginosa*.

Pseudomonas aeruginosa became a significant pathogen in the late 1960s, causing approximately 17% of cases of nosocomial respiratory tract infection and 11% of cases of bacteremia (3). It was a serious threat to patients with impaired host defenses, including those with extensive burn wounds (27), cystic fibrosis, or severe neutropenia. In a study of cancer patients with *Pseudomonas* bacteremia, many of whom had severe neutropenia, only 14% survived their infection (35). In a series of 12 studies of bacteremia caused by gram-negative organisms completed before 1976, mortality rates varied from 37% to 77% (4).

The polymyxins such as colistin were the first antibiotics that were highly active against *P. aeruginosa* in vitro, but they were not very effective clinically. For example, the rate of recovery from *Pseudomonas* bacteremia in persistently neutropenic cancer patients treated with polymyxins was less than 25%, and similar results were observed in patients with burn wound sepsis (35). It is difficult to explain the favorable response to colistin compared to the responses to the other antibiotics tested in this study. In a study of *Pseudomonas* bacteremia in cancer patients conducted at the M. D. Anderson Cancer Center in the 1960s, the response rate to polymyxins was only 24%, whereas it was 14% among the 21 patients treated with other antipseudomonal agents. Of interest, 33% of the patients were already receiving polymyxin when *Pseudomonas* was initially isolated from their blood. In a study by Curtin et al. (7), only 41.7% of the patients with *Pseudomonas* bacteremia responded to polymyxins. A possible explanation for the poor response in the 1960s may be due to improper dosing and/or the failure to diagnose the *Pseudomonas* bacteremia, which led to the delayed initiation of antipseudomonal therapy. Also, it is possible that patients receiving colistin monotherapy in this study actually continued to receive other antipseudomonal agents to

which the organisms were resistant in vitro. Although it was considered ineffective, the combination of these agents with colistin may have enhanced the patient outcome.

Potential therapeutic indications for colistin have been reported, and three studies have assessed its use in the ICU (1, 22, 30). Levin et al. (19) reported a 58% response rate in a series of 57 patients. Markou et al. (22) also reported clinical cures in 73% of patients, but it is difficult to draw a conclusion about the efficacy of colistin in their study because most of the patients received other antipseudomonal agents. Unfortunately, over the years, strains of *P. aeruginosa* have acquired mechanisms that convey resistance to antibiotics (10). Recently, strains have emerged that are resistant to multiple classes of antibiotics and in some cases to all available therapy. Some strains have been susceptible only to the polymyxins in vitro (26).

Multiple studies have suggested that polymyxins are effective and safe therapy for infections caused by these MDR strains. However, the role of these antibiotics has not been definitively established. Most studies have included only a small number of patients and the polymyxin was administered in combination with several other different antibiotics (30, 32). MDR has been defined as in vitro resistance to from as few as three classes of antibiotics to as many as all classes except polymyxins (1, 25). In some studies all beta-lactams have been combined into one class, whereas in other studies penicillins, cephalosporins, monolactams, and carbapenems have been considered separate classes (4, 34). In this study, MDR was defined as resistance to at least three of five classes, which included aminoglycosides.

This study differed from other studies reported in the literature in that all patients had underlying cancer. Sixty percent of the patients had hematological malignancies and 40% were neutropenic during their infection. Nearly half (48%) of the patients had polymicrobial infections, which typically have a poorer prognosis. As in other series, more than half of the patients were treated for their infection in an ICU. There were no statistically significant differences in these variables between the group treated with colistin and the group not treated with colistin (the control group).

In our study 16 (52%) of the 31 patients treated with colistin experienced a clinical response, whereas 20 (31%) of 64 patients treated with other antipseudomonal agents experienced a clinical response, which is comparable to the results of other studies reported in the literature (11, 18, 19, 20). A more favorable outcome of a mortality rate of only 21% was reported in a study from Israel of 82 patients with MDR *P. aeruginosa* infections, but the therapies used were not mentioned (1). In our study, after adjusting for the potential confounders, we found from a multiple logistic regression analysis that patients receiving colistin were three times (95% CI, 1.1 to 7.6 times) more likely to experience an overall response than patients in the control group. Patients with pneumonia and bacteremia typically experienced fewer responses than patients with UTIs and wound infections. Only patients with pneumonia and bacteremia received colistin; hence, they would be expected to respond less frequently. However, the overall response rate was higher for the colistin group, and colistin-containing regimens were more effective against bacteremia and pneumonia.

Among the patients receiving monotherapy, multiple logistic regression analysis showed that patients in the colistin group were more likely than patients in the control group to experience a clinical response (61% and 26%, respectively; $P = 0.005$) and microbiologic response (61% and 34%, respectively; $P = 0.013$). Most of the comparators in the control group received beta-lactam antibiotics or quinolones that were active against the MDR *P. aeruginosa* isolates causing the infection. These data further support the notion that colistin is highly useful in the treatment of MDR *P. aeruginosa* in cancer patients.

Overall in our study, 15 colistin-treated patients did not experience a response and 8 (53%) died of infection; among the patients in the control group, 44 patients did not experience a response and 11 (25%) died of infection. We found a higher mortality rate among the group of patients who did not respond to colistin than among the controls who did not respond to other antipseudomonal drugs (53% and 25%, respectively). This could be explained either by the difference in the severity of the infection in the colistin group or by a late response to an antipseudomonal drug after day 6 in the control group. Furthermore, in this patient population it is difficult to attribute death to a specific cause. In the majority of cases the cause of death was multifactorial. In our study infection-related mortality was defined as the death of a patient with septicemia due to *Pseudomonas* at the time of death without any other apparent source. On the other hand, the high overall rate of mortality noted in Table 2 was most likely due to the underlying refractory diseases and the multiorgan failure.

Our study has some important limitations in that it was a small retrospective chart review study in which we were unable to assess all of the needed detailed information, which can be obtained in a well-designed prospective trial. In addition, there was no standard pattern for the selection of the antibiotics, especially in terms of the duration and combination with other antipseudomonal agents, regardless of the susceptibility patterns of the causing organisms.

In summary, our study demonstrated that colistin is highly useful as a preferred alternative agent and it was at least as effective as or even more effective than beta-lactams or quinolones in the treatment of MDR *P. aeruginosa* infection in cancer patients. Furthermore, the safety profile of colistin in this population was comparable to that of the other conventional antipseudomonal therapy. The issue of whether colistin is superior to other antipseudomonal therapy needs to be further verified through larger prospective clinical trials.

ACKNOWLEDGMENTS

No financial support has been contributed in the development of this research.

None of the authors has a conflict of interest. Issam I. Raad and Ray Y. Hachem had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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