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Non-nephrotoxic Empiric Antimicrobial Therapy in Febrile Neutropenic Cancer Patients

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We evaluated the efficacy of piperacillin–pefloxacin as a non-nephrotoxic antibiotic combination in febrile neutropenic cancer patients treated with nephrotoxic chemotherapy. 40 patients: 34 with solid tumours and 6 with non-Hodgkin lymphoma, were treated during 55 episodes with: piperacillin 4 g intravenously every 8 h and pefloxacin 400 mg intravenously every 12 h. If the patient remained febrile after 72 h, 1 g vancomycin intravenously was added every 12 h. The mean duration of neutropenia was 7 days (range 3–13). Infection was microbiologically documented in 13 episodes (8 gram-positive cocci and 7 gram-negative bacilli). Temperature became normal in 38 patients with piperacillin–pefloxacin and 12 further episodes were resolved by the addition of vancomycin. 2 patients had an early change of antibiotics because of clinical deterioration, there were 2 protocol violations and 1 patient's temperature became normal after the addition of amphotericin. Neither septic death nor toxicity were observed. We conclude that this empirical treatment is active and safe and warrants further comparative trials.
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INTRODUCTION

EARLY EMPIRICAL therapy with broad spectrum antibiotic drugs in febrile neutropenic cancer patients has dramatically reduced the mortality rate from infection [1–3].

The standard combination of antibiotics in many centres associates an aminoglycoside plus a semisynthetic antipseudomonal penicillin. These combinations may exhibit synergistic activity [1–5]. However, there are two reasons for limiting such a combination: on the one hand aminoglycosides may increase renal toxicity of anticancer agents, mainly cisplatin, and induce severe acute nephrotoxicity [6], on the other hand, they have a limited activity against many of the gram-positive organisms which may emerge frequently [4, 7, 8].

The recent introduction of third generation cephalosporins, carbapenims, new 4-quinolones and monolactams has offered an opportunity to use equally broad-spectrum therapy with either single agent therapy or double drug combinations [1, 5, 7, 9–12]. The use of newer beta-lactams in monoantibiotherapy induces resistance and frequency of secondary gram-positive infections [1, 5, 7, 8].

We report here the results of an open trial using piperacillin (Piperilline, Lederle) and pefloxacin (Peflacin, Roger Bellon) in febrile neutropenic patients with the addition of vancomycin in case of persistent elevated fever after 72 h. The aim of this study was to evaluate the efficacy and the safety of such an approach in patients currently treated with potentially nephrotoxic chemotherapeutic agents.

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PATIENTS AND METHODS

Eligibility criteria included: histologically proven diagnosis of cancer, chemotherapeutic regimen combining either cisplatin or other nephrotoxic agents (ifosfamide, high-dose methotrexate), chemotherapy related granulocytopenia $\leq 500/\mu l$, single elevation of rectal temperature $\geq 38.5°C$ or three separate episodes of an elevation of rectal temperature $\geq 38°C$ within 24 h. The temperature elevation had to be unrelated to drug administration or blood transfusion. Patients with either evidence of a clinical site of infection at the inclusion examination or with a history of an allergy to penicillin were excluded from the trial. No antibiotic treatment was to be administered within the 24 h preceeding the inclusion in the trial.

Pretreatment was comprised of a complete history, physical examination, complete blood count, routine blood chemistry tests, chest radiography, urine, stool, and at least two blood cultures. If the patient had an indwelling venous catheter, blood was drawn through the catheter for one blood culture and from a peripheral vein for the other.

After the initial evaluation, antibiotherapy was started with: piperacillin 4 g intravenously every 8 h and pefloxacin 400 mg intravenously every 12 h. Patients were completely reevaluated at 72 h. If they remained febrile, vancomycin was added at a dose of 1 g intravenously every 12 h. Antibiotherapy was continued until recovery from neutropenia. In the case of an isolated organism, antibiotics were maintained for 10 days after bacteriological eradication.

Infection was classified according to the EORTC definition [3]: microbiologically documented infection if there are definite signs and symptoms revealing a site of infection that could be microbiologically proven (divided into those with and without bacteraemia); clinically documented infection is diagnosed if there are definite signs and symptoms of infection with an identifiable site but without microbiological proof; possible infection is considered if there are equivocal signs and symptoms of infection without a definable site and with negative microbio-

Table 1. Characteristics of patients

No. of patients	40
Median age (range) years	40 (17–69)
M/F	32/8
Underlying malignancy	
Solid tumour	34
Germ cell	18
Gastrointestinal tract	5
Urinary bladder	5
Ovary	3
Sarcoma	2
Neuroepithelioma	1
Non-Hodgkin lymphoma	6
Nephrotoxic chemotherapy (/m² per cycle)	
Cisplatin 200 mg	6
Cisplatin 70–120 mg	46
Methotrexate ≥ 300 mg	3
Ifosfamide ≥ 5 g	13

Table 2. Organisms isolated and sites

	Total number	Bacteraemia	Urine	Other sites
Gram-positive				
Staph. epidermidis	6	3	1	1 orbit 1 catheter*
Strep. agalactiae	1	1	—	—
Staph. aureus	1	1	—	—
Gram-negative				
Ps. aeruginosa	1	—	1	—
E. coli	2	1	1	—
K. pneumoniae	2	2	—	—
Enterobacter cloacae	1	—	1	—
Acinetobacter spp.	1	—	1	—

*Isolated surrounding the implantation site of the indwelling venous catheter.

logical data; or a doubtful infection if, in retrospect, it is believed that the febrile episode definitely did not respect bacterial infection. Bacteraemia was defined as one or more positive blood culture bottles for any organism, but at least two positive cultures were necessary to define *Staphylococcus epidermis* bacteraemia.

Response was classified as follows: a success if fever and infectious clinical signs resolved, and if the infecting microorganism was eradicated without a change in the first line association of antibiotics; a failure if the patient died during therapy, or if there was any change or the addition of any antibiotic based on an adequate clinical response.

Patients with a protocol violation were evaluated and considered as failures.

Serum creatinine and hepatic function were tested 3 times a week during treatment. Antibiotic related nephrotoxicity was defined as a serum creatinine rise of more than 40 μmol/l above the baseline value, in the absence of concomitant nephrotoxicity due to another drug or another pathology. Antibiotic-related hepatotoxicity was defined as a rise in serum aspartate and/or alanine aminotransferases to more than 2-fold the baseline value, in the absence of another cause of hepatic dysfunction.

RESULTS

Between March 1989 and August 1990, 40 cancer patients who had experienced in total 55 episodes of chemotherapy-related febrile neutropenia were entered into the trial. 34 patients had solid tumours and 6 patients had non-Hodgkin lymphoma (Table 1). 35 patients had an indwelling venous catheter, and 9 patients had a urinary catheter.

The mean duration of neutropenia in the 55 febrile neutropenic episodes was 7 days (range: 3–13 days). 15 organisms were isolated in 13 microbiologically-documented episodes (23%): 8 gram positive and 7 gram negative (3 organisms were isolated simultaneously during one episode). There were 8 episodes of bacteraemias, 5 organisms were found in urine cultures, one organism in the orbit and one in the area surrounding the implantation site of the indwelling venous catheter (Table 2). The remaining 42 episodes were classified as possible infection. There was neither clinically documented infection nor doubtful infection (Table 3).

According to the antibiogram, each organism was at least sensitive to one of the three drugs. We noted that all the *Staphylococcus* spp. were methicillin-resistant, that there was a *Streptococcus agalactiae* resistant to pefloxacin, and that one of the two isolated *E. coli* was resistant to piperacillin (Table 4). There was no breakthrough bacteraemia.

Table 3. Classification of infections and response according to EORTC criteria [3]

Classification	Number	Success (%)
Microbiologically documented	13	10(77)
Clinically documented	0	
Possible infection	42	40(95)
Doubtful infection	0	

Success was obtained in 38 episodes with the associations piperacillin–pefloxacin within 72 h (69%). 12 other episodes were resolved after the addition of vancomycin which was microbiologically justified in 5 patients. The success rate was 90% (50 episodes/55). All the positive responses were obtained at least 24 h before recovery of granulocyte count ≥500/μl.

Among the 5 remaining episodes, there were 2 true failures which necessitated an early antibiotic modification due to a clinical deterioration within 48 h after the initiation of treatment.

Table 4. In vitro *antibiotic sensitivity of isolated organisms*

Organism	Number	PIPE	PEFLO	VANCO
Staph. epidermis	5	R	R	S
Staph. agalactiae	1	S	R	S
Staph. aureus	1	R	S	S
	1	S	S	S
E. coli	1	R	S	
	1	S	S	
Ps. aeruginosa	1	S	R	
K. pneumoniae	2	R	S	
Acinetobacter spp.	1	R	S	
Enterobacter cloacae	1	S	S	

PIPE, piperacillin; VANCO, vancomycin; PEFLO, pefloxacin; S, sensitive; R, resistant.

The microbiological pattern was *Staph. epidermis* bacteraemia in the first episode and *Klebsiella pneumoniae* bacteraemia in the second. The first organism pointed out was sensitive to vancomycin and the latter was sensitive to pefloxacin. The protocol was violated in 2 cases because there was an early unjustified switch in antibiotics. One of these 2 cases presented a strain of pefloxacin sensitive *Acinetobacter* spp. isolated in the urine. The fifth patient was febrile 48 h after the addition of vancomycin, and then received amphotericin. Fever resolved after 2 days, while the patient was still neutropenic. No microorganism was found. There was no antibiotic-related toxicity.

DISCUSSION

This study shows that the association of piperacillin–pefloxacin, followed by vancomycin in case of persistent fever after 72 h, allowed an overall success rate of 90% in febrile neutropenic cancer patients.

In this population of patients with solid tumours and short-term neutropenia, the percentage of microbiologically documented infection is known to be low [5]. In our study, organisms were isolated during 13 episodes only in which the success rate reached 77%.

The classification of status of infection and the evaluation of response applied in our study were previously defined by the EORTC trials [2, 3]. Such standardisation may allow a useful comparative evaluation of different antimicrobial regimens [1].

The association of piperacillin and pefloxacin allows a broad-spectrum antibacterial coverage in neutropenic febrile patients, mainly in gram-negative infections [12]. Such an association has demonstrated synergistic bactericidal activity in *in vitro* trials [13]. The choice of this combination was also based on the antibiotic sensitivity of organisms isolated in our department during a 3-year period (1986–1989), and reported as infectious complications in neutropenic advanced germ cell tumour patients [14].

The activity and safety of new 4-quinolone compounds as part of an antibiotic combination in neutropenic patients have been confirmed by randomised trials; Chan *et al.*, found a similar overall success rate in the group of patients treated with ciprofloxacin plus netilmicin or piperacillin plus netilmicin [15]. Moreover, the susceptibility of gram-negative organisms to ciprofloxacin–netilmicin was significantly higher than their susceptibility to piperacillin–netilmicin [15]. Kelsey *et al.*, have demonstrated that the association of ciprofloxacin plus benzylpenicillin is as effective as the combination of netilmicin plus piperacillin, and affords a higher rate of bacteriological eradication [12].

In our study, gram positive infections in five episodes were well controlled by the addition of vancomycin empirically given after a 72-h interval. A short delay in therapy as a result of this "pathogen-directed" approach proved to be effective and did not aggravate morbidity [8]. However, the study by Shenep *et al.*, conducted in children, did show a high morbidity rate due to the absence of vancomycin in the first line empirical therapy [4].

Aminoglycosides are known to be potentially nephrotoxic: a significant increase in serum creatinine concentration was noted in 5–10% of adult patients treated with these antibiotics [6]. The nephrotoxicity of netilmicin combined with either ciprofloxacin or piperacillin was observed in 6.5% and 9.8% of episodes, respectively in the randomised study of Chan *et al.* [15]. Among the 46 patients treated with netilmicin and piperacillin in the study conducted by Kelsey *et al.*, 1 patient experienced acute renal failure and several patients had an elevation of their creatinine levels [12]. Furthermore, an EORTC trial revealed a 11% nephrotoxicity rate when the association of gentamycin plus cephalotin was used, and a 6% rate when amikacin was associated with carbenicillin [3].

Nephrotoxicity can be exacerbated by the addition of other nephrotoxic drugs, such as cisplatin and ifosfamide [6]. The histopathological examination of the kidneys of rats treated with tobramycin alone, cisplatin alone, or a combination of both drugs, revealed that tobramycin and cisplatin had an additive nephrotoxic effect compared with cisplatin alone [16]. Shenep *et al.*, excluded cisplatin pretreated patients from a trial which studied the effect of two antibiotic regimens containing amikacin specifically for these reasons [4].

All our patients were at high risk of experiencing renal toxicity, because they were treated by either conventional or double-dose cisplatin, ifosfamide alone or in combination with cisplatin, and high dose methotrexate (Table 1). We did not observe any nephrotoxicity among the 55 febrile neutropenic episodes. Moreover, there was no other toxicity nor any septic deaths.

Although, the real effectiveness of such antibiotherapy cannot be defined in the absence of a prospective randomised study. We feel on the basis of this experience that the association of piperacillin and pefloxacin with or without vancomycin, is an active and safe empirical antimicrobial therapy in febrile neutropenic patients. It avoids nephrotoxicity in cancer patients who are heavily treated with nephrotoxic chemotherapeutic agents.

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Phase I/II Study of Intraperitoneal Iproplatin in Patients with Minimal Residual Disease following Platinum-based Systemic Therapy for Epithelial Ovarian Carcinoma

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13 patients with minimal residual disease following platinum-based systemic therapy for epithelial ovarian cancer were treated with intraperitoneal iproplatin. A total of three cycles were given at monthly intervals. All patients had minimal residual disease (defined as < 2 cm in diameter) or positive cytology documented at second look laparotomy following systemic chemotherapy. Iproplatin was administered via a temporary dialysis catheter (n = 11) or a semi permanent Tenckhoff peritoneal dialysis catheter (n = 2). The dose of iproplatin ranged from 150 to 450 mg/m^2. No responses to therapy were documented. In this trial the major toxic side effects of iproplatin were thrombocytopenia, diarrhoea, nausea and vomiting. The maximum tolerated dose was 300 mg/m^2.
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INTRODUCTION

DESPITE SIGNIFICANT progress over the last 10 years in the management of advanced epithelial ovarian cancer, the majority of patients continue to die from their disease [1]. Even with optimal initial surgery and appropriate chemotherapy up to 30–50% of women with epithelial ovarian cancer will have residual disease identified at second look surgery [2, 3]. Moreover 30–50% of patients in pathological complete remission following chemotherapy will eventually recur. Patients with pathological complete remissions and minimal residual disease following second look laparotomies have been identified as targets for new therapeutic approaches designed to eliminate any remaining disease [4]. Pharmacological modelling studies have predicted that differences in the peritoneal versus plasma clearance for hydrophilic anti-cancer drugs should result in markedly increased intraperitoneal drug levels compared with the plasma if the drug is administered directly into the peritoneal cavity [5]. Subsequently a number of drugs have been shown to achieve large peritoneal to plasma ratios after intraperitoneal administration [6]. The greatest experience with this approach has been with using cisplatin, the single most active drug in ovarian carcinoma [7, 8]. Some 30% of patients with minimal residual disease following treatment with systemic therapy and subsequently treated with intraperitoneal cisplatin will achieve a complete remission. Its use, however, is associated with a number of severe side effects including nausea, emesis, nephrotoxicity, neurotoxicity and ototoxicity [9]. Attempts have been made to minimise these side effects by synthesising new analogues with improved therapeutic ratios. Iproplatin has been assessed in a number of studies and has been shown to have a similar activity but less toxicity than cisplatin in patients with epithelial ovarian cancer [9–11].

We conducted a phase I/II study to determine the maximum tolerated dose of iproplatin given intraperitoneally to assess local and systemic toxicity and to assess any response to therapy.

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PATIENTS AND METHODS

Patients and intraperitoneal administration

13 patients with histologically confirmed ovarian carcinoma were eligible for this study. All patients had been previously