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Selective Oral Antimicrobial Prophylaxis for the Prevention of Infection in Acute Leukaemia—Ciprofloxacin versus Co-trimoxazole plus Colistin

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On behalf of the EORTC—Gnotobiotic Project Group

230 leukaemic patients were entered into a randomised, prospective, multicentre trial of either ciprofloxacin (1 g/day) or co-trimoxazole (1920 mg/day) plus colistin (800 mg/day) for the prevention of infection during granulocytopenia. Bacteraemia due to resistant gram-negative rods occurred only in the co-trimoxazole–colistin group though both regimens were effective for selective gastrointestinal tract decontamination. However, there were fewer patients without any infective complications (31% vs. 18%: $P = 0.02$), fewer febrile days [mean (S.D.) 5.9 (1.1) vs. 8.2 (1.4): $P = 0.0242$], a lower proportion of infective events (0.9 (0.16) vs. 1.2 (0.18): $P = 0.005$) and fever occurred later (median 19 vs. 14 days: $0.025 < P < 0.05$) in the co-trimoxazole–colistin group. The choice of prophylactic regimen therefore appears to depend upon whether or not protection against gram-negative infection is required or better systemic prophylaxis overall.
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INTRODUCTION

SEVERE INFECTION remains a significant cause of death in patients undergoing remission induction therapy for acute leukaemia [1]. Efforts to prolong remission by more aggressive chemotherapy are limited by infectious complications that arise during profound granulocytopenia [2]. Damage to the mucosa induced by cytostatic chemotherapy of the upper respiratory and alimentary tracts, including the mouth, together with the use of devices to improve venous access render these patients susceptible to infection due to both normal commensal flora and nosocomial pathogens [3].

Over the past 2 decades there have been many attempts to prevent infection by means of environmental control measures and oral antimicrobial prophylaxis. From several controlled studies there emerged a variety of regimens which were effective in reducing the incidence of bacteraemia and in some cases also infective mortality [4–8]. However co-trimoxazole became the standard drug having the advantage of being active against *Pneumocystis carinii* [4]. Its lack of coverage against *Pseudomonas aeruginosa* and the emergence of resistance could be overcome by the addition of colistin [9].

The introduction of the fluorinated quinolones provided an opportunity to assess their efficacy and safety for the prevention of infection in granulocytopenic patients. These agents have good activity against Enterobacteriaceae (e.g. *Escherichia coli*, *Klebsiella pneumoniae*, *Ps. aeruginosa* and *Staphylococcus aureus*) but have virtually no useful activity against anaerobes [10]. They would therefore not be expected to have a negative impact on the ability of the resident flora to resist colonisation by foreign bacteria [11]. The experience with ciprofloxacin for the prevention of infection was encouraging [12, 13]. In particular, Dekker and colleagues showed that this drug was superior to the combination of co-trimoxazole and colistin in terms of preventing infections particularly those due to gram-negative rods [12]. We sought to confirm their findings in a multicentre setting and also to address specifically, the issue of selective decontamination. Furthermore we wished to establish how quickly effective prophylaxis could be established and for how long it could be maintained. We therefore conducted a prospective, randomised study in six centres comparing ciprofloxacin with co-trimoxazole plus colistin for the prevention of infection arising during granulocytopenia in adult patients being given remission induction therapy for leukaemia.

PATIENTS AND METHODS

Patient selection

Adults between 18 and 65 years who were undergoing first or second remission therapy for acute myeloblastic (AML) or lymphoblastic (ALL) leukaemia were entered into the study after they had given their informed consent provided that they had no history of allergy to one of the study drugs and their kidney and liver function was normal. In addition they were expected to be granulocytopenic ($< 0.5 \times 10^9/l$) for at least 1 week following cytostatic therapy and could only be entered

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once. Those who were admitted with fever and those who were already receiving antimicrobial therapy were eligible provided they were not being given any of the study drugs nor any other form of selective oral antimicrobial prophylaxis.

Study design and conduct

The study was designed to evaluate the efficacy of both regimens in preventing infection as well in selectively decontaminating the intestinal tract. The latter was conducted in two phases. Phase I was the period of decontamination covering the first week of prophylaxis. Patients entering the study while receiving parenteral therapy were excluded from this assessment. The maintenance of decontamination was assessed during the second phase (phase II) for a period of up to 5 weeks. The outcome of prophylaxis was also determined by the occurrence and onset of fever, the incidence of clinically and microbiologically documented infection, the number of days of parenteral therapy and mortality.

Patients were entered consecutively in each of the six centres as directed from a central non-participating statistical institution which held the randomisation code. The study was approved by the ethics committees in each of the centres.

Study period

Evaluation started on the day of randomisation and ended when the granulocyte count exceeded 1.0×10^9/l or after 6 weeks prophylaxis if no remission was achieved and the patient remained granulocytopenic. Treatment was discontinued if the subject experienced severe side-effects, was persistently colonised with a gram-negative rod which was resistant to the study regimen or was no longer willing or able to continue.

Oral antimicrobial prophylaxis

Patients received either ciprofloxacin 500 mg twice daily or a combination of co-trimoxazole 960 mg three times daily plus colistin 200 mg four times daily. All patients were given either amphotericin B 500 mg or nystatin 2×10^6 U three times daily as a solution whenever possible. Prophylaxis was initiated 1 or 2 days prior to cytostatic chemotherapy being given.

Anti-leukaemic chemotherapy

The treatment of leukaemia conformed to accepted standards. Patients with AML were generally given cytarabine combined with an anthracycline while those with ALL were treated with combinations comprising prednisone, vincristine and an anthracycline. Other drugs e.g. amsidine, mitoxantrone, etoposide and cytarabine at higher doses were used to manage patients in relapse or partial remission.

Microbiological investigations

Throat swabs or mouthwashes together with a sample of faeces were obtained for culture on admission and twice weekly thereafter. Organisms against which prophylaxis was expected to be effective (defined as 'target organisms') included specific pathogens e.g. β-haemolytic streptococci, *Streptococcus pneumoniae*, and the potential pathogens *Staph. aureus*, non-fermenting gram-negative rods including *Ps. aeruginosa*, *E. coli* and other enterobacteria and yeasts. All isolates were identified according to standard laboratory methods. Antimicrobial susceptibility testing was performed by means of disc diffusion and included testing of the study drugs. In the event of fever at least 10 ml of blood and other relevant samples from sites of infection were obtained for culture before starting empirical parenteral therapy.

Criteria for evaluating selective decontamination

Selective decontamination was deemed successful if any target organisms, particularly *E. coli*, which had been isolated before or within 3 days of the start of prophylaxis, had been cleared from its original site. Any target organism isolated on two or more consecutive occasions constituted failure as did the isolation of a resistant gram-negative rod at any time during the study period.

Clinical and other laboratory investigations

Patients were examined each day for signs and symptoms of infection and the body temperature was recorded at least three times daily. Fever was defined as either a single axillary reading (or its equivalent) in excess of 38.5°C or a temperature above 38.0°C sustained for more than 12 h for which a non-infectious cause had been excluded. Haematological and biochemical profiles were obtained at least once a week.

Infective events

Bacteraemia was defined as a single blood culture yielding any organism except coagulase-negative staphylococci and coryneforms in which case at least two positive cultures were required. A major infection consisted of bacteraemia or an infection of the lower respiratory tract. Septicaemia was diagnosed in patients presenting with hypotension and/or shock and was also considered to be a major infection. Infections of the upper respiratory tract including the maxillary sinuses, soft tissue including the abdomen, the skin, and urinary tract were considered to be minor infections. Patients who died within 1 week after stopping prophylaxis were recorded as deaths on study. Any fever that was not accompanied by clinical signs of infection, positive blood cultures or one which could not be otherwise explained e.g. by drugs or transfusions was classified as fever of unknown origin (FUO).

Systemic antimicrobial therapy

In the event of fever or infection patients were given empirical antibiotic therapy and prophylaxis was continued. The precise constitution of the empirical regimen was not regulated but it was expected to conform to a minimum acceptable standard. Only ceftazidime and imipenem were allowed as monotherapy. All other regimens consisted of a combination of an aminoglycoside plus either a broad-spectrum penicillin or a third-generation cephalosporin.

Documentation

All clinical and laboratory data were recorded and reported to the Statistical centre on forms designed for the purpose. These included demographic data, details of the type and status of leukaemia and its treatment, a daily temperature and drug chart together with the results of microbiological and other laboratory investigations. The reasons for ending the study was also recorded as were the date and cause of death, if it occurred, together with any adverse event.

Statistical considerations and analysis

A fixed sample design was used in which 100 evaluable patients were required for each treatment arm. A reduction in infective events from 50 to 30% by either arm would be significant at the 5% level with a power of 80%. Categorical data were compared by testing proportions and continuous data by t-tests. Each parameter is presented with its 95% confidence interval. The log-rank test was used in order to compare the

Table 1. Demographic details

	Ciprofloxacin	Co-trimoxazole plus colistin
Patients assessable	117	113
% Male	59.8	53.1
Age*	42.9 (3.0)	41.8 (2.4)
% Myeloid leukaemia	70.1	69.9
% Receiving antimicrobial therapy	17.1	19.5
Days to granulocytes $< 0.5 \times 10^9/l$*	1.9 (6.3)	−1.3 (13.1)
Days to granulocytes $< 0.1 \times 10^9/l$*	9.3 (1.3)	9.5 (1.8)
Duration of granulocytopenia (days)		
$< 1.0 \times 10^9/l$*	25.6 (2.0)	25.0 (4.6)
$< 0.5 \times 10^9/l$*	21.6 (1.7)	21.6 (2.0)
$< 0.1 \times 10^9/l$*	14.1 (1.6)	14.5 (1.8)
Duration of prophylaxis (days)*	31.9 (1.6)	31.3 (5.8)
% Days granulocytopenic on prophylaxis		
$< 0.5 \times 10^9/l$*	67.2 (4.4)	66.0 (5.0)
$< 0.1 \times 10^9/l$*	44.1 (4.5)	44.0 (4.9)

* Mean (95% confidence interval).

time-intervals to the onset of fever and the data were presented as a Kaplin–Meier plot.

RESULTS

Of 278 patients enrolled in the study, 142 were allocated to receive ciprofloxacin. 25 of these subjects were excluded from analysis since 15 had not satisfied the entry criteria (mainly having been entered twice), 7 had had less than 1 week's ciprofloxacin and the protocol was violated in 3 cases. Of 136 patients randomised to receive the combination, 12 did not fulfil the entry criteria and 11 had had less than 1 weeks prophylaxis. Thus 117 and 113 patients were assessable for ciprofloxacin and co-trimoxazole plus colistin, respectively (Table 1). Almost 70% of patients in each group had AML, most were receiving first remission induction and the average age and the sex distribution was similar. Approximately one fifth were already being given antimicrobial therapy on admission. The mean duration of granulocytopenia at both < 0.5 and $< 0.1 \times 10^9/l$ and the average duration of prophylaxis were virtually the same for both groups. Patients were also granulocytopenic for similar proportion of the time they were receiving prophylaxis.

Prophylaxis was discontinued in 47% of cases in the ciprofloxacin group upon recovery of granulocytes compared with 44% in the other group. Fewer patients receiving the quinolone remained granulocytopenic beyond 6 weeks than did those receiving the combination (15% vs. 24%) but almost the same number of treatments in each group were ended due to severe adverse events (15% vs. 14%). Colonisation with resistant gram-negative rods precipitated study withdrawal only once in each group (*E. coli* in the ciprofloxacin group and *Proteus vulgaris* in the combination group). Unremitting disease accounted for stopping treatment in 5 and 8 cases for the quinolone and combination group, respectively. 11 patients in the ciprofloxacin group were either unable or unwilling to comply with the protocol and a further 9 patients died; 2 cases of sepsis (*Xanthomonas maltophilia* and *Strep. pneumoniae*) 2 cases of mycosis (disseminated candidosis and fungal pneumonia), 2 of haemorrhage and 3 for which a cause was not established. Non-compliance was the reason for withdrawal in 9 cases in the co-trimoxazole–colistin group while 1 patient died of haemorrhage and another died without a specific cause being identified.

Table 2. First infection during prophylaxis

	Ciprofloxacin	Co-trimoxazole plus colistin
Patients assessable	117	113
None	21 (18.0)	35 (31.0)*
Fever of unknown origin	44 (37.6)	39 (34.5)
Bacteraemia	16 (13.7)	12 (10.6)
Clinically documented	36 (30.8)	27 (23.9)

n (%).
* $P = 0.02$.

Significantly more patients in the ciprofloxacin group experienced an infectious event than did those receiving co-trimoxazole–colistin [82 (3.6) vs. 69 (4.4%): $P = 0.02$: Table 2]. The difference in proportions was accounted for in the number of patients who developed a clinically documented infection since a similar number had FUO and bacteraemia as a first event. Moreover, the time-interval to the onset of first fever was shorter for patients given ciprofloxacin compared with that for those given the combination (Fig. 1) with the difference reaching significance after 20 days of prophylaxis ($0.025 < P < 0.05$). The average number of infective events was also significantly higher ($P = 0.005$) for those given ciprofloxacin [1.2 (0.18) events] than for those given co-trimoxazole plus colistin [0.9 (0.16) events]. Similarly, patients given the quinolone had more febrile days [8.2 (1.4) days] than did those in the combination group [5.9 (1.1) days: $P = 0.024$] and consequently had more days of parenteral antibiotics: 13.5 (1.8) days compared with 10.8 (2.0) days: ($P = 0.035$). There were no episodes of bacteraemia due to target organisms (gram-negative rods or *Staph. aureus*) in the ciprofloxacin group compared with 5 which occurred in the other group, each strain being resistant to cotrimoxazole (Table 3). Colonisation was not evident in either of the episodes due to *E. coli* whereas *Ps. aeruginosa* was recovered in the oropharynx at the onset of bacteraemia due to the same organism. Nine episodes due to

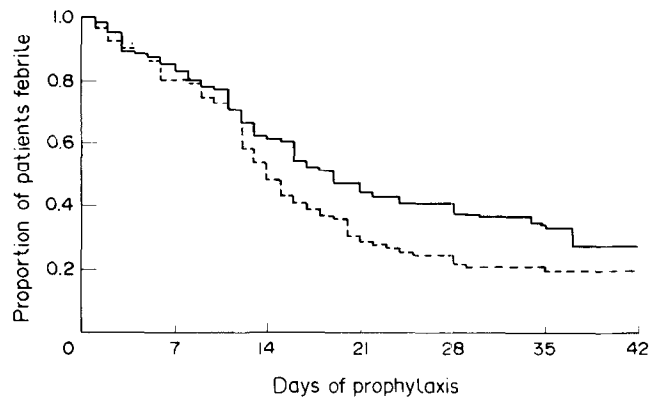

Fig. 1. Kaplin–Meier plot of days to onset of first fever. Patients given ciprofloxacin (broken line) became febrile significantly sooner (median 13 days) than those given co-trimoxazole plus colistin (solid line: median 18 days) the difference becoming significant (log-rank < 0.025, $P < 0.05$) after the 20th day of prophylaxis.

Table 3. Causes of initial bacteraemia

	Ciprofloxacin	Co-trimoxazole plus colistin
E. coli		2
Ps. aeruginosa		1
Haemophilus influenzae		1
Staph. aureus		1
Clostridium perfringens		1
Enterococcus faecalis	1	
Stomatococcus mucilaginosus	1	
'Viridans' streptococci	6	2
Coagulase-negative staphylococci	4	3
'Diphtheroids'		1
Polymicrobial		
'Viridans' streptococci + Coagulase-negative staphylococci	3	
'Viridans' streptococci + *Bacteroides* spp.	1	
Total	16	12

'viridans' streptococci occurred in the ciprofloxacin group (3 together with other organisms) compared with only 2 in the other group. 1 patient given co-trimoxazole plus colistin developed late onset bacteraemia due to pseudomonas. Candidaemia was recorded in 2 patients from each group which proved fatal in one case given ciprofloxacin prophylaxis.

More infective episodes in each class developed in the quinolone group than in those given the alternative prophylaxis (Table 4). However the proportions in each class did not differ significantly. When only infections of the upper and lower respiratory tracts and skin and soft tissue are considered, there were 65 documented in the group given the quinolone compared with 35 in other group. These infections developed after the first infective episode in 54.5% and 62.6% of cases for the quinolone and the combination, respectively although more patients given ciprofloxacin had more than two of these infections than did those in the other group ($P = 0.024$).

The rate of clearance of *E. coli* from stool samples was similar for both ciprofloxacin (mean of 1.8 (0.7) days) and co-trimoxazole plus colistin (1.7 (0.5) days) and faecal decontamination of other enterobacteria and *Staph. aureus* was achieved in 97% and 95% of cases, respectively. The majority of patients also remained free of these organisms throughout the entire study period in both oral (92% for ciprofloxacin vs. 93% for the other group) and faecal samples (95% for the quinolone vs. 92% for the combination). Persistent colonisation occurred in only one case in each group (*E. coli* with salmonellae in the quinolone group and *Pr. vulgaris* in the other group). Yeast recovery was somewhat higher in oral samples from patients given co-trimoxazole–colistin compared with those of the other group (42.7 vs. 31.8%) but similar for faeces (37.4 vs. 36.2%, respectively).

Table 4. Total infective episodes during prophylaxis

	Ciprofloxacin	Co-trimoxazole plus colistin
Total infective events	146 (%)	102 (%)
Major infections		
Septicaemia	1 (0.7)	1 (0.9)
Bacteraemia	17 (11.6)	13 (12.7)
Lower respiratory tract	27 (18.5)	19 (18.6)
Minor		
Skin/soft tissue	23 (15.8)	12 (11.8)
Upper respiratory tract	16 (11.0)	12 (11.8)
Urinary tract	3 (2.1)	1 (0.9)
Fever of unknown origin	56 (40.4)	44 (43.1)

Table 5. Adverse reactions

	Ciprofloxacin	Co-trimoxazole plus colistin
Any side effect	35 (29.9)	41 (36.3)
Rash	21 (18.0)	25 (22.1)
Gastrointestinal	7 (6.0)	10 (8.9)
Other	6 (5.1)	6 (5.3)

n (%).
Note: some patients had more than one side effect.

More patients who had received the combination were affected by adverse reactions (Table 5) than were those who were given ciprofloxacin but the incidence of rashes and other reactions was similar and the differences did not reach statistical significance.

DISCUSSION

This investigation was designed as a comparative study of two different regimens for the prevention of infection in patients with acute leukaemia who were undergoing intensive chemotherapy. The principle means of reducing the risk of infection was assumed to be by selective decontamination of the alimentary tract and in this regard both regimens performed equally well there being only one failure in each group that was due to colonisation with resistant gram-negative rods. The clearance rate of *E. coli* indicates that decontamination is likely to be rapid and follow-up surveillance confirms that selective decontamination is successfully maintained. Colonisation with yeasts affected about a third of patients but without any apparent consequences for infection. However 5 patients given co-trimoxazole plus colistin developed bacteraemia due to target organisms which were resistant to co-trimoxazole. The two episodes of bacteraemia due to *E. coli* clearly indicate failure of gut decontamination despite their absence in stool cultures obtained within a few days of bacteraemia. Whether or not the episode of bacteraemia due to *Ps. aeruginosa* is considered a failure it serves as a reminder that oral colonisation with this organism continues to be a major risk factor for sepsis even though infection due to this organism is less common than before [14].

The incidence of bacteraemia overall was lower than that reported to occur in similar patient populations [6, 15]. This may have been due to method of detection since the frequency and size of samples significantly influence the detection rate of bacteraemia [16]. Only the minimum volume of blood obtained for culture was controlled in this study, local priorities having made further uniformity impossible. Also our definition of bacteraemia due to coagulase-negative staphylococci was possibly too restrictive. In future studies samples from both a vein and a central venous catheter should be cultured, preferably using a quantitative method since this is important in diagnosing bacteraemia related to venous access devices [17]. The majority

of bacteraemic episodes were nevertheless due to gram-positive cocci rather than gram-negative rods which is consistent with the general shift from gram-negative to gram-positive bacteria mentioned earlier [18]. This trend is probably not the direct result of prophylaxis but rather a consequence of changes relating to the widespread use of intravascular devices [19] for venous access and the intensity of chemotherapy [20, 21]. However there appears to be a greater propensity for bacteraemia due to 'viridans' streptococci to develop in patients given ciprofloxacin which probably reflects the marginal susceptibility of these bacteria to quinolones as a whole [10, 11]. On the other hand, patients given co-trimoxazole also develop bacteraemia due to 'viridans' streptococci resistant to the drug [22] and therefore the phenomenon may simply be a reflection of the ease with which selection occurs as a result of prophylaxis.

Respiratory tract, skin and soft tissue infections, as a group, accounted for the lower efficacy of ciprofloxacin. These were primary events in only half of cases and were not caused by the principal target organisms namely gram-negative rods or *Staph. aureus*. Ciprofloxacin might not have given effective cover since in these settings gram-positive organisms were more likely to have been involved and, at least *in vitro*, the minimum inhibitory levels border on the achievable tissue levels at these sites [23]. 2 cases of pneumocystis pneumonia occurred off-study after 9 weeks of granulocytopenia during which time they had received ciprofloxacin as well as broad spectrum antibiotics. These together with the fatal episode of pneumococcal pneumonia appear to highlight a deficiency of quinolones which is a cause for concern when considering prophylaxis for patients at a higher risk of developing these sorts of infections such as those with cell-mediated immune deficiency. The occurrence of side-effects overall was slightly higher in patients given co-trimoxazole plus colistin but this was rarely a reason for discontinuation. That patients given ciprofloxacin developed a skin rash almost as often as patients given co-trimoxazole was quite unexpected. However leukaemic patients appear to have a higher than expected incidence of side effects to antimicrobials in general [24] which might also extend to the quinolones.

Compliance was not monitored directly, but appeared satisfactory since *E. coli* was successfully suppressed in both groups and patients completed an average of one month's treatment during which time the colonisation rate remained below 10%. Nevertheless, patients may be more likely to take two tablets of ciprofloxacin daily rather than the more complicated regimen of co-trimoxazole and colistin.

The lower incidence of infective events in the co-trimoxazole group was surprising and in marked contrast to that reported by Dekker and colleagues [12]. The study designs were to a large extent comparable and patients in both studies were similar in terms of underlying disease and cytostatic treatment. The incidence of FUO and minor infections as a whole was also similar as was the time of onset of fever and the proportion of study days that parenteral antibiotics were given. Both studies are also in accord insofar as ciprofloxacin affords favourable protection against gram-negative rods. The only clear disparity relates to the duration of granulocytopenia. Most patients in the Utrecht study experienced two periods of granulocytopenia, each of about 3 weeks duration presumably with a short recovery interval in between while those in the present study experienced a single continuous episode. Patients recovering from granulocytopenia would therefore be unlikely to develop soft tissue and respiratory tract complications whereas those with persistent, profound, granulocytopenia continue to be at risk [25]. Our data seem to confirm this and suggest that ciprofloxacin might only offer advantage in the short term whereas co-trimoxazole continues to offer benefit. It might therefore be fruitful to consider combining the two agents or modulating prophylaxis beginning with the quinolone and ending with co-trimoxazole.

Irrespective of the merits of one regimen compared with another, there are several reasons, some highlighted by the results of this study, for reappraisal of the general issue of antimicrobial prophylaxis during granulocytopenia. For instance, the incidence of gram-negative bacteraemia was low as was mortality attributable to infection. Also, despite prophylaxis, 4 of every 5 individuals received broad-spectrum antibiotics, half for fever of unknown origin and half for documented infection of which almost a third were due to gram-positive bacteria. Thus the original goal of prophylaxis may have been achieved but current circumstances have altered significantly. Many of the risk factors that prevailed when studies of infection prevention were first undertaken no longer obtain. Remission rates have improved considerably [26] and modern approaches to empirical therapy offer a greater than 95% chance of survival [15, 27]. In addition, the increasing prominence of gram-positive cocci as causes of bacteraemia poses new challenges not only for prevention and therapy but also raises the issue of their significance as pathogens [18]. In conclusion, the choice between ciprofloxacin or co-trimoxazole with colistin is far from clear and appears to depend upon whether or not protection against gram-negative infection is required or better systemic prophylaxis overall.

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Vinblastine in Metastatic Renal Cell Carcinoma: EORTC Phase II Trial 30882

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32 patients with metastatic renal cell carcinoma (MRCC) who had had no prior chemotherapy received vinblastine 0.15 mg/kg intravenously once weekly for 6 weeks, thereafter every second week, provided no major toxicity. Dose modifications were based on haematological and neurological side-effects. Only one complete response was observed among 26 evaluable patients (response rate: 4%; 95% confidence interval: 0–20%). 4 out of 29 patients developed grade 3 leukopenia. Grade 3 peripheral neurotoxicity was recorded in 2 patients. 2 patients had grade 3 alopecia. Vinblastine has no major significance on the clinical management of MRCC.
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INTRODUCTION

THE EFFICACY of chemotherapy in metastatic renal cell carcinoma (MRCC) has been limited [1, 2]. Vinblastine has been reported to be the most active drug [3] with claimed response rates up to 25% [4]. However, not all older trials meet the strict criteria of a phase II study. Therefore the EORTC Genitourinary Group decided to re-evaluate the efficacy of weekly bolus injections of vinblastine in MRCC.

PATIENTS AND METHODS

From 1988 to 1990 eight institutions entered 32 patients with measurable MRCC into the EORTC phase II trial 30882 (Table 1).

Patients were eligible for the trial if they had shown progression of bidimensionally measurable metastases from renal cell carcinoma during the 2 months preceding the trial entry. Other eligibility criteria were: age below 65 years, performance status (WHO): 0 or 1, adequate renal and liver function, no previous chemotherapy, whereas prior hormone treatment and immuno-modulating therapy was allowed provided that all treatment had been stopped for at least 4 weeks before trial entry. Informed consent was obtained from all the patients.

Treatment

Vinblastine 0.15 mg/kg was injected into a line of a running normal saline infusion, once every week for 6 weeks. Thereafter