

ORAL VERSUS INTRAVENOUS EMPIRICAL ANTIMICROBIAL THERAPY FOR FEVER IN PATIENTS WITH GRANULOCYTOPENIA WHO ARE RECEIVING CANCER CHEMOTHERAPY

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ABSTRACT

Background Intravenously administered antimicrobial agents have been the standard choice for the empirical management of fever in patients with cancer and granulocytopenia. If orally administered empirical therapy is as effective as intravenous therapy, it would offer advantages such as improved quality of life and lower cost.

Methods In a prospective, open-label, multicenter trial, we randomly assigned febrile patients with cancer who had granulocytopenia that was expected to resolve within 10 days to receive empirical therapy with either oral ciprofloxacin (750 mg twice daily) plus amoxicillin-clavulanate (625 mg three times daily) or standard daily doses of intravenous ceftriaxone plus amikacin. All patients were hospitalized until their fever resolved. The primary objective of the study was to determine whether there was equivalence between the regimens, defined as an absolute difference in the rates of success of 10 percent or less.

Results Equivalence was demonstrated at the second interim analysis, and the trial was terminated after the enrollment of 353 patients. In the analysis of the 312 patients who were treated according to the protocol and who could be evaluated, treatment was successful in 86 percent of the patients in the oral-therapy group (95 percent confidence interval, 80 to 91 percent) and 84 percent of those in the intravenous-therapy group (95 percent confidence interval, 78 to 90 percent; $P=0.02$). The results were similar in the intention-to-treat analysis (80 percent and 77 percent, respectively; $P=0.03$), as were the duration of fever, the time to a change in the regimen, the reasons for such a change, the duration of therapy, and survival. The types of adverse events differed slightly between the groups but were similar in frequency.

Conclusions In low-risk patients with cancer who have fever and granulocytopenia, oral therapy with ciprofloxacin plus amoxicillin-clavulanate is as effective as intravenous therapy. (N Engl J Med 1999; 341:312-8.)

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COMBINATIONS of β -lactams and aminoglycosides or monotherapy with ceftazidime or a carbapenem has been recommended as standard empirical therapy for fever in patients who have granulocytopenia as a result of cancer chemotherapy.^{1,2} A number of prognostic factors have been identified, the most important of which

are the type and stage of the underlying disease and the aggressiveness of cytotoxic chemotherapy.³⁻¹¹ Both factors have a strong influence on the duration and severity of granulocytopenia. As compared with patients who have granulocytopenia for an extended time, those in whom the duration of granulocytopenia is short may be at lower risk for infectious complications, are more likely to have a response to empirical antimicrobial therapy, and may require a different approach to the management of fever. For patients at low risk, simplified approaches may include early discharge from the hospital, the use of outpatient therapy, the substitution of narrow-spectrum antibiotics or oral agents, or the use of oral therapy alone.¹²⁻²⁰ Oral therapy has advantages over intravenous therapy, since it does not require intravenous-access devices; it can potentially be given on an outpatient basis, which would reduce exposure to nosocomial pathogens; it may improve the quality of life; and, if it is as effective as intravenous therapy, it might lead to substantial cost savings. The feasibility and safety of oral therapy, however, have been addressed by only a few small, single-center studies.¹⁶⁻²⁰

We undertook this trial to determine whether oral empirical therapy for fever is safe and effective in low-risk patients with granulocytopenia and whether it is equivalent to intravenous therapy. Ciprofloxacin and amoxicillin-clavulanate were chosen for oral therapy. Both agents are well absorbed, and the combination provides satisfactory coverage against gram-negative enteric bacilli and gram-positive cocci.²¹⁻²⁵ We compared this regimen with the combination of intravenous ceftriaxone and amikacin, which is reported

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*Participants in the trial are listed in the Appendix.

to be as effective as the widely used combination of ceftazidime and amikacin in febrile patients with granulocytopenia.²⁶

METHODS

Study Design and Population

Between October 1995 and November 1997, patients with solid tumors, lymphoma, or chronic leukemia who were at least five years of age were evaluated for enrollment at 25 hospitals. To be eligible, patients had to have fever, as defined previously,^{26,27} and granulocytopenia (defined as fewer than 1000 granulocytes per cubic millimeter) that was expected to last no more than 10 days. The limit of 10 days was based on an earlier retrospective analysis of risk factors for infectious complications.⁴ Patients were excluded if they had undergone allogeneic bone marrow or stem-cell transplantation; had received antibacterial agents within seven days before enrollment; had allergies to the study drugs, renal failure, shock, respiratory insufficiency, or any other signs or symptoms necessitating intravenous supportive therapy; could not swallow or keep down oral medications; had a high likelihood of dying within 48 hours after starting the study; were infected with the human immunodeficiency virus; had a catheter-related infection or infection of the central nervous system; or were pregnant or lactating. Patients with a known bacterial, viral, or fungal infection also were not eligible. Patients could be enrolled only once.

All patients or their parents or guardians gave written informed consent. The protocol was approved by the protocol review committee of the European Organization for Research and Treatment of Cancer and the institutional review boards of all participating centers.

Randomization

The patients were stratified according to study center, the type of cancer (hematologic cancer or solid tumor), and the granulocyte count at entry into the study (<500 or ≥ 500 per cubic millimeter). Randomization was performed centrally. Patients were assigned to receive oral ciprofloxacin at a dose of 750 mg (15 mg per kilogram of body weight for children who weighed 40 kg or less) every 12 hours plus oral amoxicillin-clavulanate at a dose of 625 mg (15 mg per kilogram for children ≤ 40 kg) every 8 hours or intravenous ceftriaxone at a daily dose of 2 g for adults and children who weighed at least 25 kg (80 mg per kilogram for children who weighed less than 25 kg), plus intravenous amikacin at a daily dose of 20 mg per kilogram, infused over a period of 30 to 45 minutes. The dose of amikacin was adjusted on the basis of renal function.

Assessment and Monitoring

All patients were hospitalized until the fever resolved. The clinical assessments, classification of infection, definition of secondary infection, and microbiologic methods have been described previously.^{6,26,27} The definitions of specific adverse events, including nephrotoxicity, hypokalemia, and hepatotoxicity, have been reported elsewhere.^{6,26,27}

All data were monitored on site for accuracy and completeness. Case-report forms were reviewed by a data-review committee, whose members were unaware of the treatment assignments.

End Points

The primary end point of the study was the rate of success of empirical therapy. Treatment was considered to have been successful if all the following were attained without a change in the regimen: the temperature was normal for at least three consecutive days (or two days for patients with unexplained fever and rapid recovery from granulocytopenia), the symptoms and signs of infection at identifiable sites of infection had disappeared, the primary pathogen had been eradicated, and the primary documented infection had not recurred within one week after the end of

treatment. The reasons for failure have been defined previously²⁷ and also included the inability to continue taking oral medications.

Efficacy was analyzed in all patients on an intention-to-treat basis and in the patients who were treated according to the protocol (per-protocol analysis). Patients were not included in the per-protocol analyses if their fever was found to be unrelated to infection or if there was a protocol violation (e.g., the duration of therapy was too short, the treatment regimen was modified without an adequate reason, or the patient was discharged before the fever resolved). In the intention-to-treat analysis, success was defined as resolution of fever without a change in the regimen. Secondary end points included the time to the resolution of fever, the time to a change in the regimen, the reasons for change, the time to discontinuation of any antimicrobial therapy, and survival through day 30 after randomization.

Statistical Analysis

We assumed that among the patients who could be evaluated the rate of success in the intravenous-therapy group would be 80 percent.²⁶ The null hypothesis was that the absolute difference in the success rates between the two groups would exceed 10 percent. Rejection of the null hypothesis was required to conclude that the regimens were equivalent. Using an alpha level of 5 percent and a power of 80 percent and assuming that 10 percent of the patients would not be able to be evaluated, we calculated that a sample of 560 patients would be required.²⁸

We planned two interim analyses, with stopping rules defined according to the Pocock adjustment, to compare safety in the two groups.²⁹ We also planned to compare the rates of success at the first interim analysis. We used a stopping rule that specified a level of significance of 0.005 according to the O'Brien and Fleming approach.³⁰ The analyses were conducted by a data-review committee whose members were unaware of the patients' treatment assignments.

The first interim analysis, which was performed in April 1997 and included 196 patients, indicated that there was no reason for early termination of the trial, but it revealed a higher-than-expected overall rate of success among the patients who could be evaluated (88 percent). Because of the possibility that the number of patients required had been overestimated, the data-review committee decided that an additional interim analysis of efficacy was needed. This analysis was performed in September 1997, included 263 case-report forms, and revealed that the boundary for claiming equivalence in the two treatment groups had been reached ($P < 0.003$ for stopping the study; $P < 0.001$ at the interim analysis). According to simulated studies with boundaries for stopping derived from an alpha spending-function approach, the effect of this additional analysis on the probability of a type I error was negligible.^{31,32} Bayesian calculations indicated a very small probability that the finding of equivalence would be reversed if the study was continued until the required number of patients was enrolled.³³ Therefore, we decided to end the trial in November 1997, at which time 370 patients had been enrolled.

Base-line characteristics were compared with use of chi-square tests for homogeneity or for trend or with use of Fisher's exact tests, if required. Mann-Whitney tests were used for the comparison of continuous variables. We compared the rates of success with use of the chi-square statistic proposed by Dunnett and Gent as a means of showing equivalence.³⁴ Given the group sequential design, nominal levels of significance were adjusted to maintain a P value of ≤ 0.05 as an overall indicator of statistical significance. Point estimates of success rates with confidence intervals were adjusted according to the method of Brunier and Whitehead.³⁵ Since adjusted estimates were very similar to unadjusted values, only the latter are presented. The Kaplan-Meier method was used to estimate the time to various events, and the results were compared by means of log-rank tests. All P values are two-sided.

We assessed the potential confounding effect of a number of covariates on the success rate and the time to the resolution of fever by including the base-line variables in univariate and multi-

variate logistic-regression models and Cox proportional-hazards models. The relations between the success rate and both the type of infection and duration of granulocytopenia were also assessed.

RESULTS

Characteristics of the Patients

A total of 370 patients were enrolled, of whom 17 were subsequently found to be ineligible and were excluded from the analysis (9 patients in the oral-therapy group and 8 in the intravenous-therapy group). Three patients had no fever, three did not have granulocytopenia, three could not receive oral therapy, two were allergic to the study drugs, one was enrolled twice, one did not provide informed consent, one had granulocytopenia that was not expected to resolve within 10 days, one had septic shock at presentation, one had received antibacterial agents within 7 days before randomization, and one had renal failure at presentation. Thus, a total of 353 patients were analyzed.

The two groups were well balanced with respect to demographic and clinical characteristics (Table 1). The median duration of granulocytopenia after randomization was 4 days (range, 1 to 18). Nineteen percent of the 146 patients for whom the exact duration of granulocytopenia was known had granulocytopenia for more than the expected 10 days. Most patients had profound granulocytopenia at the onset of fever (Table 1). The absolute granulocyte count did not drop below 500 per cubic millimeter in 25 patients (13 in the oral-therapy group and 12 in the intravenous-therapy group). Forty-two patients (12 percent) had bacteremia, and 87 (25 percent) had documented infections without bacteremia, most of which involved the respiratory tract.

Efficacy

Sixteen of the 177 patients assigned to oral therapy (9 percent) and 25 of the 176 patients assigned to intravenous therapy (14 percent) could not be evaluated in the per-protocol analysis (Table 2). The majority were excluded because of a protocol violation. The reasons for a change in the regimen were inadequate in the case of 22 patients (10 in the oral-therapy group and 12 in the intravenous-therapy group). The duration of therapy was too short in the case of two patients (one in each group), and the dose of study drug was inadequate in two (one in each group). One patient in the oral-therapy group and seven in the intravenous-therapy group were excluded because their fever was not related to infection; one and three, respectively, because the clinical response could not be assessed; one and one because they withdrew consent; and one in the oral-therapy group because of adverse effects.

The rates of success were similar in the two groups (Table 2). Among the patients who could be evaluated, treatment was successful for 138 of the 161 patients who received oral therapy (86 percent; 95 per-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ORAL THERAPY (N=177)	INTRAVENOUS THERAPY (N=176)
Sex — M/F	75/102	83/93
Age — yr		
Median	52	52
Range	5–85	7–83
Children — no. (%)	2 (1)	3 (2)
Underlying disease — no. (%)		
Solid tumor	120 (68)	121 (69)
Hematologic cancer	57 (32)	55 (31)
High-dose chemotherapy with peripheral-blood stem-cell support — no. (%)	25 (14)	16 (9)
Onset of fever while at home — no. (%)	113 (64)	115 (65)
Granulocyte count at randomization — no. (%)		
500–999/mm ³	19 (11)	19 (11)
100–499/mm ³	57 (32)	68 (39)
<100/mm ³	101 (57)	89 (51)
Duration of granulocytopenia — days		
After randomization†		
Median	4	4
Range	1–18	1–18
Total‡		
Median	6	7
Range	2–38	2–19
Treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor — no. (%)	108 (61)	115 (65)
Intravenous catheter before randomization — no. (%)	66 (37)	77 (44)
Oral mucositis at randomization — no. (%§)		
Grade 1	33 (19)	30 (17)
Grade ≥2	22 (12)	25 (14)
Type of primary documented infection — no. (%)		
Bacteremia	24 (14)	18 (10)
Infection without bacteremia¶	45 (25)	42 (24)
Microbiologically documented	14	15
Clinically documented	31	27
Antimicrobial prophylaxis before randomization — no. (%)		
<i>Pneumocystis carinii</i>	18 (10)	14 (8)
Antiviral	7 (4)	10 (6)
Antifungal	29 (16)	29 (16)

*There were no significant differences between the two groups.

†Values were missing for eight patients in the oral-therapy group and nine patients in the intravenous-therapy group.

‡Values were missing for 105 patients in the oral-therapy group and 102 patients in the intravenous-therapy group.

§The severity of oral mucositis was determined according to the criteria of the World Health Organization. Grade 1 denotes mild, and grade 2 moderate.

¶The sites of documented infections were the respiratory tract (16 patients in the oral-therapy group and 12 patients in the intravenous-therapy group), the urinary tract (10 and 11, respectively), and other sites (19 and 19, respectively). There were 27 patients with bacterial infections and 2 with primary viral infections.

TABLE 2. EFFICACY OF THERAPY.

TYPE OF ANALYSIS	ORAL THERAPY	INTRAVENOUS THERAPY	ADJUSTED P VALUE*
	(N=177)	(N=176)	
	no. with successful treatment/ total no. (%)		
Per protocol†	138/161 (86)	127/151 (84)	0.02
Intention to treat	141/177 (80)	135/176 (77)	0.03

*The P values for equivalence were adjusted for the results of the two interim analyses.

†Forty-one patients could not be evaluated because they had fever unrelated to infection (1 in the oral-therapy group and 7 in the intravenous-therapy group), because of protocol violations (12 and 14, respectively), or for other reasons (3 and 4, respectively). Other reasons were a clinical course that precluded evaluation of the response to therapy (four patients), withdrawal of consent (two patients), and withdrawal due to toxic effects (one patient).

cent confidence interval, 80 to 91 percent) and for 127 of the 151 patients who received intravenous therapy (84 percent; 95 percent confidence interval, 78 to 90 percent; absolute difference between groups, 2 percent; 95 percent confidence interval, -6.3 percent to 9.6 percent; P=0.02 after adjustment for the two interim analyses).

The results of the intention-to-treat analysis were similar (Table 2). Treatment was successful in 80 percent of the patients in the oral-therapy group (95 percent confidence interval, 73 to 86 percent) and 77 percent of those in the intravenous-therapy group (95 percent confidence interval, 70 to 83 percent; adjusted P=0.03).

Efficacy differed according to the type of infection, the duration of granulocytopenia, and the granulocyte count at randomization (Table 3). The rates of success were low among patients with bacteremia and those with prolonged granulocytopenia, regardless of the treatment they received. After the 25 patients whose granulocyte counts did not drop below 500 per cubic millimeter were excluded from the analysis, the rates of success were 79 percent in the oral-therapy group (129 of 164 patients) and 77 percent in the intravenous-therapy group (127 of 164). Logistic-regression analyses confirmed that there were no significant differences between the groups, even after adjustment for the type of infection and for the duration of granulocytopenia after randomization.

Among the patients included in the per-protocol analysis, six died of primary infection (two in the oral-therapy group and four in the intravenous-therapy group). One patient in each group died of bacteremia due to study-drug-susceptible *Escherichia coli*, one patient in the oral-therapy group and two patients in the intravenous-therapy group died of septic shock

TABLE 3. EFFECT ON EFFICACY OF THE TYPE OF INFECTION, DURATION OF GRANULOCYTOPENIA, AND GRANULOCYTE COUNT AT RANDOMIZATION, ACCORDING TO THE INTENTION TO TREAT.

VARIABLE	ORAL THERAPY	INTRAVENOUS THERAPY
	no. with successful treatment/ total no. (%)	
Type of infection		
Bacteremia	13/24 (54)	9/18 (50)
Gram-negative organism	6/11	7/12
Gram-positive organism	7/11	2/5
Polymicrobial	0/2	0/1
Documented infection without bacteremia	35/45 (78)	28/42 (67)
Microbiologically documented	11/14 (79)	7/15 (47)
Urinary tract infection	7/10	6/11
Other	4/4	1/4
Clinically documented	24/31 (77)	21/27 (78)
Respiratory tract	11/13	10/12
Other	13/18	11/15
No documented infection*	93/108 (86)	98/116 (84)
Duration of granulocytopenia after randomization†		
<4 days	63/74 (85)	61/71 (86)
4-7 days	64/76 (84)	60/78 (77)
>7 days	9/19 (47)	9/18 (50)
Granulocyte count at randomization		
500-999/mm ³	18/19 (95)	15/19 (79)
100-499/mm ³	49/57 (86)	51/68 (75)
<100/mm ³	74/101 (73)	69/89 (78)

*Patients with no documented infection included those with unexplained fever suspected of being due to infection (107 in the oral-therapy group and 109 in the intravenous-therapy group) and those with fever considered to be unrelated to infection (1 and 7, respectively).

†Values were missing for eight patients in the oral-therapy group and nine in the intravenous-therapy group.

after the development of unexplained fever, and one patient in the intravenous-therapy group died of viral pneumonia. Three of the deaths (one in the oral-therapy group and two in the intravenous-therapy group) occurred within three days after randomization, two deaths (one in each group) occurred within four to seven days, and one death occurred on day 11.

According to the per-protocol analysis, six patients in the oral-therapy group (4 percent) were unable to continue oral therapy. In 7 patients in the oral-therapy group (4 percent) and 13 patients in the intravenous-therapy group (9 percent), treatment was unsuccessful because of clinical deterioration. Bacterial resistance was the primary reason for treatment failure in eight patients in the oral-therapy group (including three with persistent or breakthrough bacteremia) and six patients in the intravenous-therapy group. Persistent or breakthrough bacteremia was caused by two strains of fluoroquinolone-resistant *E. coli* and two streptococcal strains that were susceptible in vitro to amoxicillin-clavulanate.

Outcome

In the intention-to-treat analysis, overall survival was similar in the two groups (Table 4). At day 30, 95 percent of the patients with adequate follow-up were alive; eight patients in the oral-therapy group and nine in the intravenous-therapy group had died. The causes of death in these 17 patients were primary infection in 6 patients (2 in the oral-therapy group and 4 in the intravenous-therapy group) and were related to underlying disease in 9 patients (5 and 4, respectively). Death was considered unrelated to the infection or underlying disease in one patient in the oral-therapy group, in whom heart failure developed, and in one patient in the intravenous-therapy group, who died unexpectedly on day 3.

The median time to the resolution of fever was two days in both groups (Fig. 1). Multivariate analysis with the Cox proportional-hazards model confirmed that treatment was not associated with the time to resolution of fever.

If the eight patients who died before their fever resolved were included in the analysis, a total of 34 patients in the oral-therapy group and 39 in the intravenous-therapy group had a change in their treatment regimen (19 percent vs. 22 percent; 95 percent confidence interval for the absolute difference between groups, -11 percent to 5 percent; $P=0.58$). The proportion of patients whose therapy was modified without adequate reason was similar in the two groups (Table 4). There was no significant difference in the time to the first change in the regimen or in the time to the discontinuation of any antimicrobial therapy (Table 4). Probably because of the short duration of granulocytopenia, secondary infections developed in very few patients in either group (Table 4).

Adverse Events

Approximately one third of the patients in each group had adverse events, and the frequency of treatment-related events was similar in the two groups (Table 4). More patients in the oral-therapy group than in the intravenous-therapy group reported diarrhea or other gastrointestinal symptoms (26 patients vs. 4 patients). Conversely, only patients in the intravenous-therapy group had adverse events associated with intravascular catheters (11 patients), nephrotoxicity (4 patients), and hypokalemia (4 patients). Treatment-related hepatotoxicity was rare (two patients in the oral-therapy group and three in the intravenous-therapy group). No signs or symptoms of arthritis were reported.

DISCUSSION

In this study of low-risk patients with cancer who had fever and granulocytopenia, the rates of success and outcomes were similar with orally administered antimicrobial drugs and an intravenously administered regimen. Given the open-label design of this

TABLE 4. OUTCOME OF THERAPY AND ADVERSE EVENTS ACCORDING TO THE INTENTION TO TREAT.*

VARIABLE	ORAL THERAPY (N=177)	INTRAVENOUS THERAPY (N=176)
Overall survival — no. surviving/ no. with adequate follow-up (%)†		
Day 7	172/176 (98)	171/176 (97)
Day 30	163/171 (95)	162/171 (95)
Death before resolution of fever — no. (%)	3 (2)	5 (3)
Reasons for change in regimen — no. (%)‡		
Serious complication or clinical deterioration		
With microbial resistance	3 (2)	1 (1)
Without microbial resistance	9 (5)	17 (10)
Microbial resistance without serious complication or clinical deterioration	3 (2)	7 (4)
Other	8 (5)	1 (1)
No adequate reason documented	11 (6)	13 (7)
Time to first change in regimen — days‡§		
Median	3.5	3.0
Range	0–6	0–10
Time to discontinuation of any anti- microbial therapy — days¶		
Median	6	6
Range	1–61	1–37
Secondary infection — no. (%)	13 (7)	11 (6)
Adverse events — no. (%)		
Any	64 (36)	55 (31)
Related to treatment	29 (16)	27 (15)
Serious	16 (9)	13 (7)

*There were no significant differences between the two groups.

†Follow-up with respect to survival was inadequate for six patients in the oral-therapy group and for five patients in the intravenous-therapy group. These 11 patients have been excluded from the analysis of overall survival.

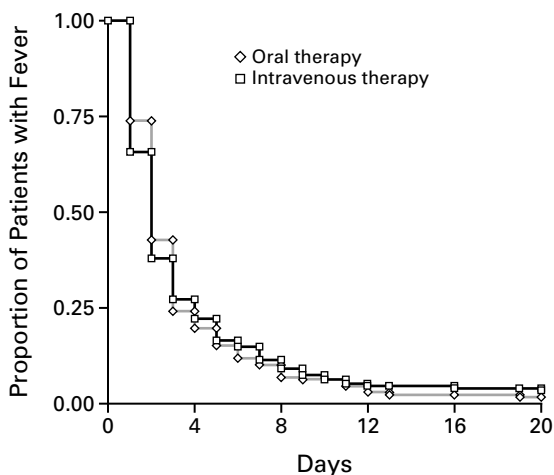
‡Treatment was modified in two of the three patients in the oral-therapy group and four of the five patients in the intravenous-therapy group who died before their fever resolved.

§Values are Kaplan–Meier estimates, with 143 censored observations in the oral-therapy group and 137 in the intravenous-therapy group.

¶Values are Kaplan–Meier estimates, with six censored observations in each group.

trial, there was the possibility that there might have been earlier and more frequent changes in the oral-therapy regimen aimed at averting treatment failure. However, modifications without adequate reason were no more frequent in the oral-therapy group than in the intravenous-therapy group, and the times to a change in therapy were similar. The few cases in which therapy was discontinued for reasons directly related to oral administration were considered treatment failures.

Previous studies that reported similar rates of success for oral and intravenous therapies were not designed to evaluate the equivalence of the treatments. The numbers of patients were small, resulting in wide confidence intervals for differences between the treat-



No. AT RISK						
Oral therapy	177	43	18	8	4	3
Intravenous therapy	176	48	20	9	8	7

Figure 1. Kaplan–Meier Estimates of the Time to the Resolution of Fever in Low-Risk Patients with Cancer Who Had Granulocytopenia and Were Receiving Oral or Intravenous Empirical Therapy.

The median time to the resolution of fever was two days in both groups (P=0.97 by the log-rank test).

ment groups.¹⁸⁻²⁰ Thus, although no significant differences were found, such differences certainly could not be ruled out. Our study was specifically designed to assess whether the regimens were equivalent, and we believe that our results provide convincing evidence that oral empirical therapy can be as effective as intravenous therapy.

We used simple criteria to identify low-risk patients: we excluded patients who had received allogeneic bone marrow or peripheral-blood stem-cell transplants, those with acute leukemia, those in whom granulocytopenia was expected to last longer than 10 days, and those with shock or any other condition that required intravenous supportive therapy or precluded oral intake of drugs. The small percentage of patients in whom treatment was modified because of complications or clinical deterioration (8 percent), the low rate of secondary infections, and the low mortality rates in the two groups indicate that these criteria were appropriate.

Despite the fact that we selected a low-risk population, 12 percent of the patients had bacteremia, and several had unexpectedly prolonged granulocytopenia. The rates of successful treatment among the patients with these risk factors were low in both groups. Although it might be possible to refine the criteria for predicting low risk, detailed prediction models will be more useful for making decisions about whether management should be handled on an inpatient

basis or an outpatient basis, rather than whether oral therapy or intravenous therapy should be used.³⁶ In fact, we were unable to identify a subgroup of patients in whom oral therapy appeared to be associated with lower rates of response than was intravenous therapy.

Our findings must not be interpreted as suggesting that oral empirical therapy administered on an outpatient basis should be the new standard of treatment for low-risk patients. Our patients were hospitalized until fever resolved. Although several trials of outpatient management have reported favorable results,^{18,20} only one study seems adequately designed to address this question.³⁷ Further carefully designed studies are needed to specify the conditions under which outpatient therapy will be an acceptable and perhaps the preferred choice. In any case, the establishment with each patient and family of careful rules for contacting the physician is essential.

An increase in resistance to fluoroquinolones has been reported among patients with cancer who received these drugs for prophylaxis.^{38,39} In our study we found that the risk of failure due to bacterial resistance was small among recipients of fluoroquinolones and was similar to that among patients receiving other antimicrobial drugs after the institution of standard intravenous combination therapy. The development of resistance to fluoroquinolones, both in the community and in hospitals caring for patients with cancer, however, will be a critical determinant of the future efficacy of oral therapy for fever and granulocytopenia.

An observation of some concern was the occurrence of persistent and breakthrough bacteremia in the oral-therapy group. Remarkably, the streptococcal isolates from initial and follow-up blood cultures were susceptible in vitro to amoxicillin. Careful clinical observation is required with regard to the development of such infection. With more experience, it will be useful to reassess the indication for and dosage of amoxicillin–clavulanate in patients with fever and granulocytopenia who are treated with an oral fluoroquinolone. Newer fluoroquinolones with enhanced activity against gram-positive pathogens might obviate the need for oral combination therapy. Tolerance of the regimens is an important issue, since it is likely that treatment with amoxicillin–clavulanate caused a substantial number of the gastrointestinal adverse events reported in the oral-therapy group in our study.

A working committee of the Infectious Diseases Society of America recently updated guidelines and recommended that all patients with cancer who have fever and granulocytopenia should be promptly treated with maximal doses of broad-spectrum antibiotics by the intravenous route.^{1,2} Our study provides clinical data to support the use of oral antimicrobial therapy as an effective alternative approach to empirical therapy in low-risk patients.

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APPENDIX

The participants and centers, listed according to the number of eligible patients enrolled in the trial, were as follows: *Patras University Hospital, Patras, Greece (63)* — H. Bassaris and A. Skoutelis; *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (40)* — G. Zanetti; *Institut Jules Bordet, Brussels, Belgium (35)* — F. Crokaert; *Hospital Universitario, Salamanca, Spain (27)* — D. Caballero; *St. Savas Hospital, Athens, Greece (23)* — A. Efreimidis; *National Institute of Oncology and St. Elisabeth Hospital, Bratislava, Slovak Republic (22)* — V. Krcmery, Jr.; *Evangelismos Hospital, Athens, Greece (18)* — C. Alexopoulos; *Chaim Sheba Medical Center, Tel Hashomer, Israel (17)* — E. Rubinstein; *Ibni Sina Hospital, Ankara, Turkey (16)* — H. Akan; *Hôpital Universitaire Erasme, Brussels, Belgium (11)* — J.-P. Thys; *Medizinische Universitätsklinik, Ulm, Germany (10)* — W.V. Kern; *Universitätsspital, Zurich, Switzerland (10)* — A. Schaffner and F. Follath; *Hadassah University Hospital, Jerusalem, Israel (8)* — M. Shapiro; *Zentralkrankenhaus St. Jürgenstraße, Bremen, Germany (8)* — B. Sievers; *Rabin Medical Center, Petah Tikva, Israel (8)* — M. Weinberger; *Allgemeen Ziekenhuis Middelheim, Antwerp, Belgium (7)* — R. de Bock; *National Cancer Institute, Genoa, Italy (6)* — C. Viscoli and R. Rosso; *Hacettepe University Hospital, Ankara, Turkey (5)* — M. Akova; *Hôpitaux Civils de Charleroi, Charleroi, Belgium (5)* — J.-C. Legrand; *Centre Hospitalier Universitaire, Luxembourg, Luxembourg (4)* — R. Hemmer; *Kinderspital, Zurich, Switzerland (4)* — D. Nadal; *Hospital General y Universitario Vall d'Hebron, Barcelona, Spain (2)* — A. Estibalez; *Hôpital Avicenne, Bobigny, France (2)* — R. Lortholary and C. Larroche; *Masaryk University Hospital, Brno, Czech Republic (1)* — H. Kubsova; *Hospital Universitario La Fe, Valencia, Spain (1)* — M. Sanz; *Study Coordinators* — W.V. Kern and A. Cometta; *Data Review Committee* — R. de Bock (coordinator), A. Cometta, F. Crokaert, D. Engelhard, H. Gaya, W.V. Kern, J. Langenaeken (data manager), A. Padmos, and M. Paesmans (statistician); *Advisory Board* — T. Calandra, J. Klasterky, C. Viscoli, and S.H. Zinner; *Microbiology Reference Laboratory* — M. Galazzo and J. Bille; *Chair* — M.P. Glauser.

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