MAJOR ARTICLE

A European Organization for Research and Treatment of Cancer–International Antimicrobial Therapy Group Study of Secondary Infections in Febrile, Neutropenic Patients with Cancer

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Background. Neutropenic patients with cancer may develop several episodes of fever and infection during chemotherapy-induced myeloaplasia.

Methods. To identify risk factors for secondary infectious episodes among patients who responded to initial antibiotic therapy, we retrospectively analyzed 2 consecutive, prospective, randomized clinical trials performed by the International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer during 1991–1994.

Results. Of 1720 patients with their first episode of febrile neutropenia, 836 responded to the initial antibiotic regimen and were therefore suitable for our analysis. A secondary infection was observed in 129 (15%) of 836 patients that occurred at a median of 10 days (range, 1–28 days) after the onset of the primary febrile episode. Factors at both baseline and day 4 were analyzed. Age of >16 years (odds ratio [OR], 3.46; $P < .001$), acute leukemia in first induction (OR, 3.17; $P < .001$), presence of intravenous line (OR, 1.88; $P = .04$), severe neutropenia (defined as an absolute granulocyte count of <100 cells/mm^3) on day 4 (OR, 2.72; $P < .001$), and type of documentation of the primary episode (i.e., microbiologically documented cause or unexplained fever; OR, 2.56; $P = .001$) were found to be risk factors for secondary infection. The risk of death was higher among patients who developed a secondary infectious episode than among those who did not (5.4% vs. 1.4%; $P < .01$).

Conclusions. The clinical parameters described above may help to identify neutropenic patients at risk of developing secondary infection.

Broad-spectrum antibiotics are always given empirically for the treatment of patients with cancer who have neutropenia and fever. This practice has led to a marked reduction of infectious mortality, although it might result in overuse of antibiotics and in the emergence of drug-resistant microorganisms [1]. Aggressive antineoplastic treatment modalities result in alteration of host natural defences, such as the occurrence of severe mucositis secondary to high-dose cytosine arabinoside therapy. Use of central venous catheters may promote skin and soft-tissue infections, as well as bacteremia [2]. Successful control of initial infectious episodes of neutropenia and fever may be followed by the emergence of secondary episodes, and the knowledge of factors associated with the risk for such events may be helpful for prevention or treatment. Few studies have actually attempted to identify such variables [3–5]. The aims of the present study were to provide a description of etiologic and clinical aspects of secondary episodes in febrile, neutropenic patients with cancer who responded to an initial empirical therapy and to identify factors associated with the risk of a secondary episode.

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PATIENTS AND METHODS

The analysis was conducted on a dataset extracted from the pooled database of 2 clinical trials of empirical antibiotic therapy of febrile neutropenia in patients with hematological malignancies or with solid tumors performed by the International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer during the period of 1991–1994. The first study compared piperacillin-tazobactam plus amikacin with ceftazidime plus amikacin [6], and the second compared meropenem monotherapy with ceftazidime plus amikacin [7]. To avoid bias related to a potential dependency between outcome data, only first entries for each patient were included. In addition, we selected only patients who responded to the initial therapy for analysis, because information on this outcome in nonresponding patients is often confused and unreliable. Fever was defined as a single temperature measurement of $\geqslant$38.5°C or $\geqslant$2 measurements of $\geqslant$38.0°C within a 12-h period. Neutropenia at enrollment in the trials was defined as an absolute granulocyte count of <1000 cells/mm^3 that was anticipated to decrease to <500 cells/mm^3 within 24–48 h [6–8]. As in our standard definitions [6], a secondary infection was defined as any episode of fever and/or infection not present at the initial evaluation that developed either during empirical therapy or within 1 week after discontinuation of therapy. In the case of microbiologically documented infection, the isolated pathogen should have been different from the pathogen isolated during the primary episode. Primary infections were classified, as in our standard definitions, as microbiologically documented infections, clinically documented infections, and fever of unknown origin. Secondary infections were classified as microbiologically documented infections (with or without bloodstream infection [BSI]—that is, bacteria and/or fungi isolated from samples of blood or from other sites), viral infections, clinically documented infections (when a microbiological documentation was missing, but there were objective and detectable signs of infection), or fever of unknown origin. Microbiologically documented infections or clinically documented infections were counted as "secondary" between day 0 and day 4, because the success of initial regimen, by definition, required a minimum of 4 afebrile days.

For detection of possible associations between patients and/or infection characteristics and the occurrence of a secondary infection (yes vs. no), 2 groups of variables were considered: those assessable on day 0 (day of enrollment in the trial), and those assessable on day 4 after enrollment. Variables assessed on day 0 were age, sex, underlying disease (acute leukemia, first induction; acute leukemia in stages other than fist induction; and other), receipt of a bone marrow transplant (BMT; autologous, allogeneic, or no BMT), presence of a localized infection (in addition to fever), presence of an intravenous line, severity of neutropenia (using the level 100 cells/mm^3 as cutoff), body temperature (using the temperature 39°C as cutoff), administration of oral antibacterial (quinolone with or without penicillin, trimethoprim-sulfamethoxazole), antiviral (acyclovir) or antifungal (nystatin, amphotericin B, ketoconazole, itraconazole, or fluconazole) prophylaxis before trial, decision to continue the oral administration of these agents during empirical therapy (depending on each participating center's standard practice), use of granulocyte colony-stimulating factors, and type of empirical antibiotic regimen as allocated at randomization. Variables assessed on day 4 after enrollment included severity of neutropenia, differential granulocyte count between day 0 and day 4 (increasing, stable, or decreasing), type of documentation of the primary episode (available and recorded on day 4, based on tests performed at enrollment or immediately after), and temperature on day 4.

Criteria were those used in previous trials from our group [9, 10] or were based on the median distribution of the variable to be categorized to make groups of comparable sizes. All categories are described in tables 1 and 2. Differential granulocyte count between day 0 and day 4 was categorized as decreasing, stable, or increasing. A stable count was defined as a relative variation of <10% or as an absolute variation of <100 cells/mm^3. Temperature on day 4 was dichotomized as no fever or persistent fever. Only covariates with <10% of missing data were selected for the analysis. To make sure that we were not missing important information by mixing documented and nondocumented secondary episodes, we performed 2 analyses, including and excluding fever of unknown origin from the list of secondary episodes.

We first looked at the univariate association between the outcome and each of the considered covariates using logistic regression models. Estimated ORs were computed with 95% CIs, and likelihood ratio tests were done to test the hypothesis of an OR different from 1. Variables associated with a P value of <.3 in univariate analysis were retained to be included in the multivariate analysis to be conducted in a second step. The final models were selected using a backward-stepwise method (a P value of <.05 was necessary for the variable to remain in the model). Time to secondary infection was estimated by the Kaplan Meier method. Death rates at day 30 were compared using the χ^2 test for heterogeneity. All reported P values are 2-tailed.

RESULTS

A total of 1971 febrile neutropenic episodes were included in the 2 randomized trials. There were 1720 patients with eligible first febrile episodes, and 836 (49%) responded to the initial empirical treatment and therefore fulfilled our selection criteria. Among patients selected in the present study, 63% had received antibacterial prophylaxis, 57% had received antifungal prophylaxis, and 23% had received antiviral prophylaxis. A sec-

Table 1. Characteristics of 836 patients and univariate analysis of baseline factors associated with secondary infections.

Covariate	No. of patients	Rate of superinfection, %	OR (95% CI)	*P*
Age, years				
⩽16	192	7.3	1	
>16	644	17.9	2.76 (1.56–4.94)	.001
Sex				
Male	433	14.3	1	
Female	403	16.6	1.19 (0.82–1.74)	.36
Underlying disease				
Acute leukemia, first induction	166	30.1	3.86 (2.46–6.07)	<.001
Acute leukemia, other setting	222	15.3	1.62 (1.00–2.61)	.05
Other	448	10.0	1	
Bone marrow transplantation				
No	646	16.1	1	
Autologous	133	14.3	0.79 (0.50–1.27)	.34
Allogeneic	56	10.7	…	
Clinical site of infection				
No	537	16.9	1	
Yes	299	12.7	0.71 (0.47–1.07)	.11
Intravenous line in situ				
No	199	8.0	1	
Yes	637	17.7	2.47 (1.42–4.27)	.001
Granulocyte count, cells/mm^3				
<100	525	16.0	1	
⩾100	308	14.6	0.82 (0.53–1.28)	.39
Temperature, °C				
<39	597	15.2	0.95 (0.63–1.44)	.81
⩾39	239	15.9	1	
Oral antibacterial therapy before trial				
No	313	11.8	1	
Yes	523	17.6	1.59 (1.06–2.40)	.03
Oral antifungal therapy before trial				
No	362	11.0	1	
Yes	474	18.8	1.86 (1.25–2.78)	.002
Oral antiviral therapy before trial				
No	646	16.3	1	
Yes	190	12.6	0.75 (0.46–1.20)	.23
Growth factors received during the episode of neutropenia				
No	556	16.2	1	
Yes	278	13.7	0.82 (0.54–1.24)	.34
Oral antibacterial therapy during trial				
No	731	16.0	1	
Yes	105	11.4	0.68 (0.36–1.28)	.23
Oral antifungal therapy during trial				
No	274	9.9	1	
Yes	562	18.1	2.03 (1.29–3.19)	.002
Oral antiviral therapy during trial				
No	600	16.3	1	
Yes	236	12.6	1.22 (0.82–1.84)	.33
Empirical treatment				
Ceftazidime and amikacin	407	16.7	1	
Piperacillin-tazobactam and amikacin	159	14.5	0.84 (0.51–1.41)	.51
Meropenem	270	14.1	0.82 (0.53–1.26)	.36

Table 2. Univariate analysis using variables assessable on day 4 after the onset of fever.

Covariate assessed on day 4	No. of patients (n = 836)	Rate, %	OR (95% CI)	P
Granulocyte count, cells/mm^3				<.001
<100	408	23.0	3.47 (2.27–5.31)	
⩾100	416	7.9	1	
Differential granulocyte count				
Increasing	288	6.3	1	
Stable	424	19.1	3.54 (2.07–6.05)	<.001
Decreasing	110	25.5	5.12 (2.70–9.73)	<.001
Infection documentation				.004
CDI	225	9.3	1	
Other	611	17.7	2.09 (1.27–3.42)	
MDI	160	20.6	…	
FUO	451	16.6	…	
Fever				.60
No[a]	693	15.7	1	
Persisting	143	14.0	0.87 (0.52–1.46)	

NOTE. CDI, clinically documented infection; FUO, fever of unknown origin; MDI, microbiologically documented infection.

[a] Temperature, <38°C.

ondary infection occurred in 129 (15%) of 836 patients (95% CI, 13%–18%). There were 40 microbiologically documented infections, 14 with and 26 without BSI. In addition, there were 11 single-virus infections (9%; 8 herpes simplex virus infections and 3 cytomegalovirus infections), 39 clinically documented infections (30%), and 39 fevers of unknown origin (30%). Sites of infection in patients with clinically documented infection were the respiratory tract (including the oropharynx) in 23 patients, skin and soft tissue in 6 patients, the gastrointestinal tract in 4 patients, the intravenous device insertion site in 4 patients, and other sites in the last 2 patients. The causes of microbiologically documented infections are shown in table 3. A total of 50 bacterial or fungal pathogens were isolated, including those isolated in multibacterial and mixed infections. Of them, 25 (50%) were gram-positive bacteria, 4 (8%) were gram-negative rods, and 21 (42%) were fungi. One herpes simplex virus infection occurred concurrently with a *Candida albicans* infection and was classified as a mixed microbiologically documented infection without BSI.

The cumulative risk of secondary infections, according to the number of days after randomization, is presented in figure 1. The median time to development of secondary infection was 10 days (range, 1–28 days; interquartile range, 7–12 days). Only 8 of 129 secondary infections developed before day 5. The overall crude mortality at day 30 was significantly higher among patients with than among those without secondary infections (7 [5.4%] of 129 vs. 10 [1.4%] of 707; OR, 4.00; 95% CI, 1.49–10.71; $P = .01$). When fevers of unknown origin were excluded and only documented secondary infections were considered, the median time to infection did not change significantly (9 days; interquartile range, 7–12 days).

Analysis of factors associated with the risk of secondary infections. Table 1 presents the baseline characteristics of patients and the association of these characteristics with the risk of secondary infection in a univariate model. Among baseline factors, age of >16 years (OR, 2.76; $P = .001$), acute leukemia treated with first-induction chemotherapy (OR, 3.86; $P < .001$), acute leukemia in a stage other than first induction (OR, 1.62; $P = .05$), presence of an intravenous line in situ (OR, 2.47; $P = .001$), receipt of antibacterial prophylaxis before enrollment (OR, 1.59; $P = .03$), and receipt of antifungal prophylaxis before enrollment (OR, 1.86; $P = .002$) and during empirical therapy (OR, 2.03; $P = .002$) were all associated with an increased risk of secondary infection. Among factors assessed on day 4 after enrollment (table 2), the severity of neutropenia (OR, 3.47; $P < .001$), stable granulocyte count (OR, 3.54; $P < .001$), decreasing granulocyte count (OR, 5.12; $P < .001$), and presence of a microbiologically documented infection or a fever of unknown origin (associated with a clinically documented infection) as documentation of the primary episode (OR, 2.09; $P = .004$), were all associated with an increased risk of secondary infection.

As shown in table 4, when the data were fit in a multivariate logistic regression model on the basis of covariates assessable at randomization, adult age (OR, 3.13; $P < .001$), acute leukemia in first induction (OR, 3.62; $P < .001$), and presence of intra-

Table 3. Etiology of microbiologically documented secondary infections (MDIs) in 40 patients.

Infection class, microorganism	No. of patients
MDI with bloodstream infection	14
Single-bacterial infection	
Staphylococcus haemolyticus	2
Bacillus species	1
Corynebacterium species	1
Enterococcus faecalis	1
Streptococcus viridans	1
Multibacterial infection	
Clostridium species and Streptococcus viridans	2
Corynebacterium JK and *E. faecalis*	1
S. haemolyticus and *Staphylococcus* species	1
Fungal infection	
Candida krusei	1
Candida tropicalis	1
Candida albicans and *Candida glabrata*	1
Mixed infection: *Staphylococcus epidermidis* and *C. glabrata*	1
MDI without bloodstream infection	26
Single-bacterial infection	
Coagulase-negative staphylococci	5
Staphylococcus aureus	2
Staphylococcus species	1
Clostridium difficile	1
Escherichia coli	1
Multibacterial infection: *Pseudomonas aeruginosa* and *Enterobacter* species	1
Fungal infection	
C. albicans	3
Candida species	2
Aspergillus species	3
Aspergillus fumigatus	1
Mucor species	1
C. albicans and *C. glabrata*	1
Pneumocystis carinii	1
Mixed infection	1
Aspergillus species and *Clostridium* species	1
Alternaria species and *E. coli*	1
C. albicans and herpes simplex virus	1

venous line in situ (OR, 2.38; $P = .003$) continued to have independent predictive value. Two additional factors (absolute granulocyte count on day 4 [OR, 2.72; $P < .001$] and type of documentation [clinically documented infection vs. other; OR, 2.56; $P = .001$]) were found to also be associated with increased risk of secondary infections when the day 4 covariates were included in the model.

Analysis of factors associated with the risk of documented secondary infection. A multivariate analysis using only clinically and microbiologically documented secondary infections as dependent variables yielded similar results, with 2 differences: the presence of an intravenous line at enrollment was no longer statistically significant, whereas the administration of antiviral prophylaxis became significantly protective (OR, 0.42; 95% CI, 0.22–0.79; $P = .007$).

DISCUSSION

The clinical problem of secondary fever and infection in neutropenic patients with cancer has not been addressed very often in the medical literature. Although there has been a reference to the problem in several trials in which different antimicrobial regimens were compared, the question was specifically examined in only a few studies, which reported variable rates, probably depending on different patient populations and different definitions. In the present study, we found a rate of secondary infections of 15% among patients who were successfully treated with the empirical antibiotic treatment given at the time of randomization in the trials. This rate compared well with the one reported by Serra et al. [3], who found a rate of 12% (78 of 631 patients, with a total of 102 episodes). The only risk factors that these authors found on univariate analysis were the severity and persistence of granulocytopenia, which was assessed as the duration of granulocytopenia before the development of fever. There was no relationship between development of secondary infection and length of hospitalization, duration of previous antibiotic therapy, previous chemoprophylaxis, and presence of indwelling venous catheters. Feld et al. [4] published their data only in an abstract form. With respect to our findings, they reported a higher rate of secondary infection, which they identified in 154 (24%) of 644 severely febrile neutropenic patients who had acute leukemia or who had undergone bone marrow transplantation. The multivariate analysis indicated that longer duration of antimicrobial therapy and lack of response to empirical therapy were both independent factors for developing secondary infection, whereas an-

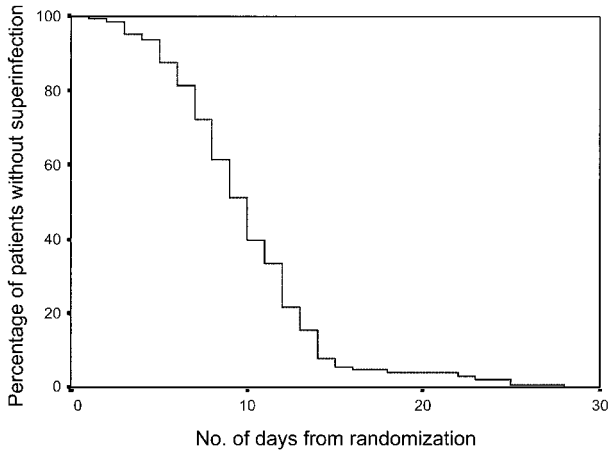

Figure 1. Time to development of a superinfection in 129 patients

Table 4. Findings of multivariate analyses of covariates at baseline and on day 4 after onset of fever.

Covariate	OR (95% CI)	*P*
Baseline covariates only ($n = 836$)		
Age, years		
<16	1	<.001
⩾16	3.13 (1.73–5.66)	
Underlying malignancy		
Acute leukemia		
First induction	3.62 (2.28–5.76)	<.001
Stage other than first induction	1.57 (0.96–2.56)	.07
Other malignancy	1	
Intravenous line		
Not present	1	
Present	2.38 (1.35–4.21)	.003
With addition of day 4 covariates ($n = 822$)		
Age, years		
<16	1	
⩾16	3.46 (1.89–6.33)	<.001
Underlying malignancy		
Acute leukemia		
First induction	3.17 (1.96–5.15)	<.001
Stage other than first induction	1.34 (0.80–2.23)	.26
Other malignancy	1	
Intravenous line		
Not present	1	
Present	1.88 (1.02–3.48)	.04
Granulocyte count on day 4, cells/mm^3		
<100	2.72 (1.72–4.28)	<.001
⩾100	1	
CDI documented as cause of fever on day 4	1	
Cause of fever other than CDI	2.56 (1.51–4.36)	.001

NOTE. CDI, clinically documented infection.

tiviral prophylaxis had a protective effect. Duration of neutropenia had no effect on the development of a secondary infection. Nucci et al. [5] prospectively evaluated 46 additional infectious episodes that developed in 333 febrile neutropenic attacks (14%). They identified 4 independent factors by multivariate analysis that were related to an increased incidence of secondary infections: longer duration of severe neutropenia (absolute granulocyte count, <100 cells/mm^3), lack of use of prophylactic quinolones, persistence of fever on day 4 of the initial regimen of empirical therapy, and presence of a central venous catheter. The mortality rate was doubled among patients with secondary infection.

In the present study, bacteria (mainly gram-positive bacteria) accounted for 58% of the 50 bacterial and fungal pathogens isolated from patients with documented infection. This was not surprising, because 63% of our patients had received quinolone or trimethoprim-sulfamethoxazole prophylaxis, which provided efficacy against gram-negative bacteria but not full efficacy against gram-positive bacteria. Fungal pathogens were isolated from 19 (48%) of 40 patients with secondary documented infection, a rate lower than the rate of 67% reported by Nucci et al. [5], although it is still relevant. The difference might be explained by the fact that 57% of our patients had received oral antifungal prophylaxis, and 67% had received these agents while receiving empirical antimicrobial therapy, whereas only 17% of patients were given antifungal prophylaxis in the trial by Nucci et al. [5]. This possible explanation, however, is partially contradicted by the fact that, in our study, the predictive effect of antifungal prophylaxis was statistically significant only in univariate analysis but not in the final multivariate model.

Of the baseline factors, age of >16 years, acute leukemia as an underlying disease, and presence of an intravenous line were significantly associated with higher incidence of secondary episodes. These factors remained significant even when factors available on day 4 were included in the model. Children have always been shown to be at lower infection risk than adults, probably because of differences in underlying diseases and a better general performance status. This fact was also shown by our group recently [11]. As is widely known, patients with acute leukemia receive more-intensive chemotherapeutic regimens than do other oncological patients, and this exposes these patients to a higher risk of infectious complications [12]. Uncontrolled underlying disease at admission and longer duration of neutropenia (median, 23 days in patients with the first induction of acute leukemia, vs. 19 days in patients with acute leukemia with a stage other than first induction [$P = .01$], and vs. 10 days in the remaining patients; data not shown) might be responsible for more-frequent secondary infections in patients with the first induction of acute leukemia. Finally, intravenous catheters are a well-known source of infection, especially for gram-positive bacteria [2]. Because the initial empirical regimens for febrile neutropenic patients usually do not provide reliable coverage against most gram-positive agents, and because they even may select for resistant pathogens during therapy, it is not surprising that the patients with an intravenous catheter in place would be more likely to develop superinfections during the course or after completion of the empirical treatment regimen [13].

In the present analysis, the absolute granulocyte count at the time of development of fever (i.e., enrollment in the trials) was not predictive of the risk of secondary infection. On the contrary, patients who were persistently and severely granulocytopenic on day 4 were statistically more prone to develop secondary infections. These findings compared well with those reported by Nucci et al. [5], although the same finding was not reported by others [4]. Because persistent and severe neutropenia is a well-known predisposing factor for infection in febrile, neutropenic patients with cancer [14], it could be an expected risk factor for secondary infections as well. The use of

growth factors was not associated with the development of secondary infections. However, we did not find any relationship between underlying disease, severity of neutropenia, and use of growth factors. At study entry, similar numbers of patients in all 3 underlying disease categories had neutropenia (including those with severe neutropenia, defined as a granulocyte count of <100 cells/mm^3). Furthermore, there was no difference in the proportion of patients who received growth factors in various categories of patients (data not shown).

Administration of antiviral prophylaxis was excluded from the final model when all secondary infections (including fever of unknown origin) were considered. However, interestingly, it was shown to play a significant role when only documented infections were evaluated. This issue has been addressed previously in the literature with conflicting results. Lonnqvist et al. [15] reported that oral acyclovir prophylaxis may reduce the rate of microbiologically documented infection in patients with acute leukemia, whereas Bergmann et al. [16] more recently noted that acyclovir prophylaxis postponed the development of fever, but it did not have an effect on the duration of fever or on the need for antibiotics and did not reduce the incidence of bacteremia. It is possible that antiviral prophylaxis may protect the integrity of oral mucosa by preventing herpetic stomatitis.

Several prognostic factors influencing mortality have been described in febrile, neutropenic patients with cancer [9–11, 17]. In accordance with previous reports [3, 5], the present results confirm that development of a secondary infection is a significant additional factor for increased mortality among these patients.

In the present study, we analyzed secondary infections only in patients who responded to the initial empirical regimen. This means that our results cannot be applied to all febrile and neutropenic patients. However, when considering confusion regarding the discrimination between primary and secondary or associated episodes in nonresponding patients, we believe that this was the only way to address the problem with the available data. Our study has been able to identify some clinical parameters that, if present, might alert physicians to a possible risk of new complications. Obviously, only ad hoc, prospective epidemiological studies might be able to give more insight on this problem.

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