The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies

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Background and Objectives. It is now evident that patients experiencing febrile neutropenia induced by chemotherapy do not constitute a homogeneous group. With increasing accuracy it is now possible to identify low-risk patients for whom less intensive and more convenient treatment may be appropriate.

Design and Methods. In a cohort of such patients with hematologic malignancies, we prospectively validated the usefulness of the risk-index of the Multinational Association of Supportive Care in Cancer (MASCC) in identifying patients at low risk for the development of serious medical complications. Moreover, we studied the feasibility and safety of early discharge of these low-risk patients 24 hours after fever defervescence with subsequent oral antibiotic therapy.

Results. Of the 279 episodes of febrile neutropenia included, 105 (38%) had a MASCC risk-index score indicating low risk. Serious complications were reported in connection with 111 (63%) high-risk and 16 (15%) low-risk episodes ($p<0.0001$). The risk-index identified low-risk patients with a specificity, sensitivity and positive predictive value of 87%, 58%, and 84%, respectively. A substantial proportion of the low-risk patients (36%) were considered ineligible for oral therapy, while the remaining 67 (64%) received oral antibiotic treatment following discharge from the hospital 24 hours after defervescence. Upon final evaluation, 64 of the discharged patients (95%) remained afebrile, only three required readmission and there was no mortality in this group.

Interpretations and Conclusions. The MASCC risk-index is a valuable tool for identifying febrile neutropenic patients at low risk for complications. Oral antibiotic treatment following discharge from the hospital 24 hours after defervescence offers a safe and cost-effective alternative to the conventional management of carefully selected low-risk patients.

Key words: febrile, neutropenia, oral antibiotic, risk index, hematologic malignancy.

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Infection continues to be the most common complication associated with neutropenia induced by chemotherapy.[1,2] Over the past several decades, there has been substantial progress in the treatment of hematologic malignancies including the development of new chemotherapeutic agents and other therapeutic modalities such as stem cell transplantation. Unfortunately, most of the treatment strategies used are associated with profound suppression of innate and/or acquired immunity and thus further increase susceptibility to infections.[3] Prompt hospitalization of patients exhibiting chemotherapy-induced neutropenia together with fever and initiation of empirical intravenous therapy with broad-spectrum antibiotics has been the standard care provided for the past 30 years.[2] Indeed, if such patients are not treated or treated inappropriately, their mortality rate within the first 48 hours may be as high as 50%.[4,5] However, it has become evident that patients with febrile neutropenia are not a homogeneous group and do not run the same risk of developing life-threatening complications or death.[6,7] Accordingly, individual risk assessment of febrile neutropenic patients with cancer is gradually becoming an integral part of their initial evaluation, allowing better classification of patients for different therapeutic strategies, ranging from ambulatory antibiotic treatment to more intensive treatment with a combination of antibiotics together with early antifungal therapy.[8,9]

A number of different models based on the characteristics demonstrated by patients at onset of febrile neutropenia have been designed to enable clinicians to assign patients to high- or low-risk groups, attempting to identify those patients with the greatest chance of recovering without serious medical complication.[6,7,10,11] The prognostic factors included in such a model developed by the Multinational Association of Supportive Care in Cancer (MASCC)[12] are presented in Table 1. Patients with a score of ≥21 generally have fewer serious medical

complications (6%) and a low rate of mortality (1%). One limitation of the MASCC study is that it included relatively few patients with active acute leukemia who typically display neutropenia of longer duration and generally have a higher risk of complications and mortality than do patients treated for solid tumors. The MASCC risk-index score has been validated prospectively[12,13] and is now recommended for use as an aid in choosing therapeutic strategies for individual patients.[2,8,14] There are different treatment options for low-risk patients other than conventional hospitalization and intravenous administration of antibiotics during the entire febrile episode. These options include early discharge following initial stabilization in the hospital[15–17] and out-patient treatment with oral antibiotics alone.[18–22]

To our knowledge, the clinical application of the MASCC risk-index score has not been evaluated prospectively. Therefore, the present study was designed to perform such an evaluation in patients with hematologic malignancies. The accuracy with which this score can identify those patients with febrile neutropenia who are at low risk of developing serious medical complications was estimated. In addition, we also examined the feasibility, efficacy and safety of employing early discharge together with oral antibiotic therapy to treat such low-risk patients, at the same time, and importantly, identifying factors which render a switch to oral therapy inappropriate.

Design and Methods

Patients

All adult patients admitted to our center from November 2003 through April 2005 for treatment of fever and neutropenia associated with chemotherapy for hematologic malignancies were included in this study. Fever was considered to be present if the temperature measured orally or by tympanic thermometry was ≥38° C on two occasions at least 4 hours apart during a 24-hour period or was ≥38.5° C on a single occasion. Neutropenia was defined as an absolute neutrophil count (ANC) of ≤0.5×10^9/L. Upon admission a history was taken, physical examination performed, and MASCC risk-index score calculated according to Table 1 for each patient. A complete blood cell count, routine biochemical analyses, chest radiography, and urine analysis were performed prior to the initiation of therapy. At least one blood sample for aerobic and anaerobic culture was taken from a central venous catheter lumen (if present) and another from a peripheral vein. When coagulase-negative staphylococci were recovered, bacteremia was considered as significant only if the isolates were detected in two or more blood specimens and with the same antibiotic sensitivity pattern.

After initial evaluation, all patients were hospitalized and received broad-spectrum intravenous antibiotics in accordance with local and international recommendations[2,23] until the fever subsided. The patients were monitored daily for clinical complications. Serious medical complications were defined as the development of one or more of the following: hypotension, respiratory failure, renal failure, requirement for intensive care, confusion or altered mental status, congestive heart failure, loss of blood necessitating transfusion, arrhythmias requiring treatment, fungal infection, allergic reaction, or death. Complete blood cell counts and routine biochemical analyses were repeated every 24-48 hours until the fever and neutropenia were resolved or until the patient was discharged and subsequently treated with oral antibiotics (see below). Chest radiography and cultures of blood samples were repeated and invasive diagnostic procedures performed whenever clinically indicated.

Table 1. The risk-index score designed by the Multinational Association of Supportive Care in Cancer (MASCC) for the identification of low-risk patients at the onset of febrile neutropenia.

Prognostic factor	*Score*[1]
Extent of illness[2]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
No previous fungal infection	4
No dehydration	3
Out-patient at the time of fever onset	3
Age < 60 years	2

[1]A risk-index score ≥21 indicates that the patient is likely to be at low risk for complication and morbidity, [2]choose one item only. This scoring system was adapted from that proposed by Klastersky et al.[12]

Modifications of the intravenous treatment regimen, including the addition of vancomycin and empirical treatment with antifungal agents, were made in accordance with local and international recommendations.[2,23,24] Accordingly, vancomycin was added in cases with documented infection with methicillin-resistant staphylococci or ampicillin-resistant enterococci or when such an infection was clinically suspected and the patient was not responding to the initial antimicrobial therapy. Empirical antifungal therapy was added in patients with sustained fever and neutropenia despite antibiotic therapy for more than 4-5 days. Mortality related to infection and 4 weeks after the onset of fever were both recorded. The initial episode of fever was classified as either infectious (determined clinically or microbiologically) or of unknown origin (FUO), as described previously.[23]

Low-risk patients who developed shock, hemodynamic instability, catheter-related infection, microbiologically verified infection with a multi-resistant microorganism (e.g. coagulase-negative staphylococci or *Enterococcus faecium*) which demanded continued intravenous antibiotic therapy, or invasive fungal infection were not considered for oral therapy. Nor were patients who experienced abdominal pain, nausea/vomiting, diarrhea, and/or inability to swallow oral medications (Table 2). All other low-risk patients were transferred from intravenous to oral antibiotic therapy 24 hours after their fever had subsided.

Table 3. Recommendations concerning the choice of oral antibiotics to be administered to low-risk patients following discharge 24 hours after subsidence of fever.

Diagnosis/localization of infection	*Antibiotics recommended Condition after subsidence of fever*	
	Still neutropenic (ANC≤0.5×10⁹/L)	*No longer neutropenic (ANC > 0.5×10⁹/L)*
Skin/soft tissue infection	Ciprofloxacin+ clindamycin	Clindamycin
Pneumonia/ bronchitis	Ciprofloxacin+ amoxicillin	Ciprofloxacin+ amoxicillin
Anal ulceration/infection	Ciprofloxacin+ amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid
Dental/oral cavity infection	Ciprofloxacin+ amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid
Fever of unidentified origin	Ciprofloxacin+amoxicillin	Ciprofloxacin
Positive culture results	Individual treatment	Individual treatment

Table 2. Clinical conditions/reasons considered to render 38 of 105 low-risk patients ineligible for oral treatment with antibiotics.

Clinical condition/reason	*Number of patients*
Infection with multi-resistant bacteria, verified microbiologically*	11
Invasive fungal infection, clinically suspected or proven#	8
Gastrointestinal complications and swallowing difficulties	4
Generally deteriorating condition	4
Central venous catheter infections	3
Deep abscess of soft tissue	2
Endocarditis	1
Previously included twice in the study	1
Psychiatric disease	1
Refusal to take oral antibiotics	1
Unspecified	2

**Coagulase-negative staphylococci (n=9), Enterococcus faecium (n=1) and resistant Klebsiella species (n=1); #including one case of Pneumocystis jiroveci pneumonia, three cases of invasive pulmonary aspergillosis, and four cases of pneumonia in which fungal infection was suspected, but never confirmed to be the cause.*

The choice of which oral antibiotic agents to administer was made on the basis of a pre-defined recommendation which took into consideration the nature of the febrile episodes, the site of the infection, and our own local epidemiological data and clinical experience[25] (Table 3). The first dosage of oral treatment was administered at hospital, after which, if no acute complications arose, the patients were discharged and subsequently treated and monitored as out-patients. Oral antibiotic treatment was continued for 5 days, irrespective of the ANC.

The out-patients were instructed to return immediately to the hospital if they developed a fever, or were unable to tolerate the oral medication, or if their overall condition deteriorated. These patients had telephone access to the study team and the hematology unit during the day and to acute health-care facilities at all times. Three days after discharge, patients made a follow-up visit to the hematology day-care unit and final evaluation of the treatment outcome was carried out either 4 weeks after subsidence of fever or at the time of initiation of the next chemotherapy cycle.

Oral treatment was considered to have failed if the patient died, had a relapse of fever, or any other clinical deterioration resulting from infection. Anti-bacterial prophylaxis is not used routinely in our center. Prophylactic use of acyclovir, valaciclovir, fluconazole and trimethoprim-sulfamethoxazole was permitted. Growth factors (G-CSF) were not used routinely, but were allowed when given as a part of the CHOP-14 treatment protocol.[26] The same patient could be re-entered into the study only one more time, provided that his/her neutrophil count had returned to normal between the episodes of neutropenic fever. Hospitalization costs were estimated on the basis of mean daily cost per routine in-patient (including medical, nursing, paramedical services, general services and basic medication) as determined by the economy department for hematology patients at our hospital. The reduction in the duration of the hospitalization achieved by early discharge of low-risk patients was determined by comparing the length of the actual hospital stay after subsidence of fever (24 hours) with the estimated hospital stay associated with conventional treatment strategies. International recommendations regarding the duration of intravenous antibiotic treatment after defervescence (a minimum of 7 days for neutropenic patients and 2 days if the neutropenia had been resolved or if the patient had FUO) were adhered to.[2,27,28] Accordingly, the reduction in the duration of hospitalization was estimated to be 6 days for patients who were still neutropenic and 1 day for patients with FUO and/or resolved neutropenia at fever defervescence.

Patients receiving oral therapy for the first time were asked to complete a questionnaire, designed specifically for this study, 3 days after discharge. This questionnaire included 12 items concerning the patient's satisfaction with the care received (Table 4). This instrument was adapted from a previous study[29] and tested with regarding to the relevance and clarity of the questions on ten patients prior to initiation of the study.

Written informed consent was obtained from all of our subjects and our experimental protocol was approved prior to the start of the study by the regional ethics committee.

Statistical analysis

The data are expressed as means (± standard deviation) or as medians (range). The χ^2 or Fisher's exact test was applied as appropriate, to compare proportions and Student's t-test or, when appropriate, the Mann-Whitney U-test was used for comparison of means. A 2×2 table was employed for calculation of sensitivity and specificity. A positive predictive value was calculated in order to estimate the rate of uncomplicated recovery among low-risk patients, together with a negative predictive value for high-risk patients predicted to develop serious medical complications. In addition, first

Table 4. The satisfaction of 36 low-risk patients receiving oral antibiotic therapy with their case.

Question/statement	*Responses*
To be responded to by "yes" or "no", number of "yes" answers (%)	
Would you prefer to be treated with oral antibiotics during any subsequent episode of fever?	34 (94)
Did you wish to stay in hospital a longer time?	3 (8)
Mean degree of agreement with the statement using a scale ranging from 0 = strongly disagree to 6 = strongly agree	
I find it convenient to take antibiotics orally	5.7
I find it easy to take antibiotics outside the hospital	5.6
I feel confident about taking my medication outside of the hospital	5.3
I find it easy to take all doses of the oral antibiotics prescribed	5.4
I am capable of performing my daily activities without problems	5.1
I feel good on my current antibiotic treatment	5.3
I believe that I receive the support I need from the medical service for my treatment	5.7
I am satisfied with the staff continuity at my return visits	5.2
I am satisfied with the information provided concerning the oral antibiotics	5.2
Overall I am satisfied with my present treatment with oral antibiotics	5.7

Table 5. Characteristics of high- and low-risk patients experiencing febrile neutropenic episodes.

Characteristics	*High-risk*	*Low-risk*
Number of episodes/ number of patients	174/132	105/81
Age in years, median (range)	60 (21-85)	57 (20-87)
Male/female	94/80	63/42
Underlying disease*		
acute leukemia#	89 (51)	52 (50)
non-Hodgkin's lymphoma	46 (24)	37 (35)
multiple myeloma	32 (18)	7 (6)
Hodgkin's lymphoma	5 (2)	4 (4)
chronic leukemia	2 (1)	5 (5)
Central venous access device*		
implanted subcutaneous port system	98 (56)	56 (53)
central venous catheter	48 (27)	15 (14)
High-dose chemotherapy with stem cell support*	42 (24)	4 (4)
Prophylaxis*		
trimethoprim-sulfamethoxazole	12 (6)	8 (7)
valaciclovir	84 (48)	51 (48)
fluconazole	87 (50)	49 (46)
Growth factors (G-CSF)*	50 (29)	38 (36)

**Number of episodes (% of the total number of episodes); #including acute myeloid leukemia, acute lymphoblastic leukemia and myelodysplastic syndrome in transformation to acute leukemia.*

episodes of neutropenic fever (i.e. occurring in patients not previously included) were analyzed separately to exclude any effect on results caused by repeated inclusion. A p value of <0.05 was considered to be statistically significant.

Results

Patients' characteristics

During the 18-month study period, 191 adult patients who developed a total of 279 episodes of fever and neutropenia following chemotherapy were treated at our unit. All of these patients were being treated for hematologic malignancies, predominantly acute leukemia (50% of the total number) and non-Hodgkin's lymphoma (30%). All patients demonstrated severe neutropenia at the time of onset of their fever, with a mean ANC of 0.18 (±0.14)×10^9/L, and ANC ≤0.1×10^9/L in 178 (67%) episodes. The mean duration of neutropenia, from the point of inclusion in this study to achievement of an ANC >0.5×10^9/L, was 11 days (±10 days). In 217 (77%) of the episodes the involved patient had a central venous catheter. During 88 (31%) of the episodes granulocyte colony-stimulating factor was given in addition to the assigned treatment, and 46 (16%) patients received high-dose chemotherapy in combination with autologous stem cell support.

Table 6. Clinical evaluation of febrile neutropenic episodes in high- and low-risk patients.

Clinical evaluation, n (%)	*High-risk group*	*Low-risk group*	*p value*
Diagnosis of infectious episode			
fever of undetermined origin (FUO)	55 (32)	47 (45)	0.018
clinically documented infection	41 (24)	19 (18)	0.37
pneumonia*	20 (11)	20 (19)	0.08
microbiologically documented infection	78 (44)	39 (37)	0.20
with bacteremia	67 (38)	36 (34)	0.47
without bacteremia	11 (6)	3 (3)	0.26
Signs and symptoms of infection at the time of presentation			
only fever	92 (53)	63 (60)	0.24
respiratory tract symptoms	33 (19)	24 (26)	0.43
cellulitis	17 (10)	13 (14)	0.35
gastrointestinal tract symptoms	27 (16)	4 (4)	0.001
Pathological chest X- ray examination	40 (22)	17 (16)	0.17
Laboratory findings			
ANC ≤0.1×10^9/L	105 (60)	73 (70)	0.07
ANC at inclusion (10^9/L), mean (±SD)	0.19 (±0.14)	0.17 (±0.13)	0.20
duration of neutropenia, days, mean (±SD)	11.6 (±11)	10 (±8)	0.65
duration of fever, days, mean (±SD)	8.4 (±7)	6.1 (±5)	0.004

**not including pneumonias with microbiologically documented infections; ANC: absolute neutrophil count; SD: standard deviation.*

The characteristics and clinical features of the patients included in this study are summarized in Tables 5 and 6.

Microbiologically documented infection was the most common cause of fever (42% of all febrile episodes), with bacteremia dominating (38%). The causative pathogens identified in the bloodstream are documented in Table 7. In 60 (22%) episodes infection was indicated clinically, but no causative pathogen could be isolated. Pneumonia accounted for 66% of all clinically verified infections. In 36% of all febrile episodes the cause of fever could not be determined.

The MASCC risk-index score

At the time of presentation 105 (38%) of the febrile episodes occurring in 81 patients were associated with low risk according to the MASCC risk-index score (risk score ≥21) and 174 (62%) episodes (in 132 patients) were high-risk (risk score < 21). A higher percentage of the patients in the high-risk group had central venous catheters (p=0.001) and had been administered high-

Table 7. Pathogens identified in the bloodstream of high- and low-risk patients in connection with 103 episodes of febrile neutropenia.

Micro-organism, n	*High-risk group*	*Low-risk group*
Coagulase-negative staphylococci	15	9
E. coli	17	5
α hemolytic streptococci	15	7
Enterococcus spp.	10	1
Klebsiella spp.	9	2
Staphylococcus aureus	5	4
Enterobacter spp.	5	2
Clostridium spp.	1	1
Pseudomonas aeruginosa	2	0
Stenotrophomonas maltophilia	2	0
Streptococcus agalactiae	2	0
Other	7	3
Total	90	34

dose chemotherapy with autologous stem cell support (p=0.0001) (Table 5). The proportion of patients with acute leukemia, the mean duration of neutropenia and the incidence of bacteremia were similar in the two groups (p>0.05). The mean duration of fever was significantly longer in high-risk patients than in low-risk patients (p=0.006) (Table 6). Serious medical complications were reported in association with 111 (63%) high-risk and 16 (15%) low-risk episodes (p< 0.0001) (Table 8). Thus, the overall rate of misclassification was 28%. The specificity, sensitivity and positive and negative predictive values of the MASCC risk-index score regarding the development of medical complications were calculated to be 87%, 58%, 84% and 64%, respectively.

Modification of the initial antibiotic treatment

Modification of initial therapy involving a single antibiotic was required significantly more often among high-risk (130/174) than among low-risk (48/105) episodes (p<0.001). The mean number of days of intravenous antibiotic use (per number of antibiotics times days) was also higher in high-risk (16±11 days) than in low-risk episodes (11±10 days) (p=0.003). Supplementation with empirical antifungal therapy was clinically indicated in 35 high-risk and 13 low-risk episodes (p=0.05).

Early discharge of low-risk patients with subsequent oral antibiotic treatment

In 38 low-risk episodes, patients were not eligible for oral antibiotic treatment and were excluded from this aspect of the study. The reasons for exclusion are summarized in Table 2. This sub-group of low-risk patients had a mean MASCC score of 23 (±1.7) which was comparable with that of other low-risk patients (p=0.90). However, these patients had longer mean durations of neutropenia (12±8.9 versus 8±6.7 days), and of fever (9±6.3 versus 4±3.5 days) and higher incidences of serious medical complications (34% versus 4%), bacteremia (55% versus 19%) and acute leukemia (71% versus 37%) than did low-risk patients considered eligible for oral antibiotic treatment (p≤0.01).

Table 8. Incidence of medical complications in high- and low-risk patients.

Medical complication, n (%)	*High-risk*	*Low risk*	*p value*
Hypotension (systolic blood pressure < 90 mm Hg and/or a need for pressure support)	37 (21)	3 (3)	< 0.0001
Respiratory failure, with hypoxia or requirement for mechanical ventilation	39 (22)	4 (4)	< 0.0001
Confusion or altered mental status	23 (13)	2 (2)	0.0009
Congestive heart failure and/or arrhythmias requiring treatment	16 (9)	2 (2)	0.03
Loss of blood requiring transfusion	18 (10)	2 (2)	0.007
Renal failure requiring intervention	3 (1)	1 (1)	0.99
Disseminated intravascular coagulation	0	0	
Proven invasive or superficial fungal infection invasive pulmonary aspergillosis candidemia	49 (28) 9 (5) 1 (.5)	5 (5) 3 (3) 0	< 0.0001
Allergic reaction	25 (14)	3 (2)	0.001
Admission to the intensive care unit	10 (5)	0	0.01
Death without resolution of fever	6 (3)	1 (1)	0.26

A total of 67 low-risk episodes were followed by discharge with oral antibiotic treatment 24 hours after defervescence. One patient had to be readmitted 2 days after discharge due to recurrence of fever (failure of oral treatment). This patient was treated for bacteremia caused by *Klebsiella pneumoniae*, responded well to ceftazidime, but became febrile again upon receiving oral treatment with ciprofloxacin, despite the fact that his causative bacteria were susceptible to this antibiotic. He was subsequently treated again with intravenous antibiotics and no superinfection was detected. In connection with the clinical follow-up 2-4 days after discharge from the hospital, all remaining patients (99%) were afebrile and exhibited reduced symptoms of infection. One patient had to discontinue her oral antibiotic treatment because she developed diarrhea, but remained afebrile and did not require any further treatment. At the final evaluation 4 weeks after discharge, two patients had been readmitted to the hospital due to the presence of new infections. Both of these patients developed a fungal infection (one had *Pneumocystis jiroveci* pneumonia and the other invasive pulmonary aspergillosis) after their neutropenia had resolved and antibiotic treatment discontinued. The other 64 patients all remained afebrile and, since there was no mortality, the success rate of oral antibiotic treatment was 95%.

Satisfaction with care

In connection with their first inclusion in this study, 36 low-risk patients completed the questionnaire con-

cerning how they experienced their care 3-7 days after discharge from the hospital. The majority of these patients expressed satisfaction with the timing of hospital discharge, the approach to treatment, the use of oral antibiotics and the follow-up program. The patients stated that they felt confident with this treatment strategy and found it convenient (Table 4).

Toxicity

The oral treatment with antibiotics was, in general, well-tolerated. Twenty patients reported degrees of nausea, diarrhea and/or abdominal discomfort, which were, however, so mild that no modification of their oral therapy was required. One episode of moderately severe diarrhea did result in discontinuation of oral antibiotics (*see above*). During intravenous treatment with antibiotics allergic skin reactions necessitating a change of antibiotic were observed in 28 patients.

Mortality

The overall 4-week mortality rates were 5.7% (10 patients) in the high-risk group and 2% (2 patients) in the low-risk group (p=0.22). The mortality in high-risk patients caused by infection (n=6) involved septic shock in three cases, pneumonia with respiratory failure in two and invasive pulmonary aspergillosis in one patient. Both fatalities in the low-risk group were caused by infection: one 78-year old patient, excluded from oral antibiotic treatment due to a deteriorating general condition, never became afebrile and died from septic shock (*Klebsiella spp.*). The other patient (68 years old) was considered ineligible for oral treatment due to a catheter-related infection and was treated successfully with intravenous antibiotics, but relapsed with fever 8 days after the completion of treatment and died from clinically documented pneumonia and the progression of acute leukemia. As stated above, no mortality occurred among the patients receiving oral antibiotic treatment.

Duration of hospitalization and utilization of resources

The mean stay in the hospital, counting from the first day of fever, was significantly shorter for the patients receiving oral antibiotics (6±4 days) than for high-risk patients (16±13 days; p< 0.0001). The duration of hospitalization and intravenous antibiotic treatment was shortened by 2.2 (±1.8) days for those low-risk patients discharged early with oral antibiotic treatment. Thus, the total hospital costs per febrile episode were reduced by approximately 1600 .

Discussion

In the present investigation we found that the MASCC risk-index score is a useful tool for identifying febrile neutropenic patients with hematologic malignancies who are at low risk of developing complications. In addition, we prospectively demonstrated the feasibility of employing this risk-index, in combination with clinical observation during the initial days of intravenous therapy in the hospital, to identify low-risk patients suitable for early discharge from the hospital with subsequent oral antibiotic treatment. Our increasing efforts to improve quality of life of patients experiencing neutropenic periods as a consequence of chemotherapy, together with necessity of reducing health care costs, makes early identification of such low-risk febrile patients of considerable value. The most recent risk stratification model, designed and validated by the MASCC in a multinational, multicenter study involving more than 1100 patients with fever and neutropenia,[12] is based on easily identifiable characteristics present at the onset of fever. This makes the model applicable in daily clinical practice and, at the same time, allows standardization of patient groups included in various studies. However, of the patients included in the validation group, only 21% had acute leukemia. Consequently, application of this risk-index to patients with hematologic malignancies requires further validation and, in addition, its clinical application has not previously been evaluated prospectively.

In the current study the proportion of patients classified as high-risk (62%) was higher than in other studies (19-27%), most probably reflecting differences between groups of patients involved. Low-risk patients were identified here with a positive predictive value of 84% and a specificity and sensitivity of 87% and 58%, respectively, values which differ somewhat from those obtained in the original MASCC study (i.e., a positive predictive value of 91%, specificity of 68% and sensitivity of 71%). Our classification of being at low risk was also associated with a shorter duration of fever, higher rate of successful monotherapy and relatively low incidence of infection-related mortality. Thus, this model of risk stratification appears to be of value in the management of hematologic patients who develop febrile neutropenia following chemotherapy. Results remained the same when the analysis was restricted to first episode of febrile neutropenia per included patient (i.e. eliminating all second episodes).

The routine therapeutic approach to febrile neutropenia, involving hospitalization and administration of intravenous broad-spectrum antibiotics during the entire episode, has been questioned for many years now. Different therapeutic options have been tried with low-risk patients, among which outpatient treatment with oral antibiotics may be the most attractive, reducing hospital costs, avoiding catheter complications, improving the quality of the patient's life and reducing the risk of infection by resistant nosocomial microorganisms. This approach has been tested on hospitalized patients with neutropenia of short duration in two prospective randomized studies,[18,21] which reported an efficacy and safety comparable to those of intravenous antibiotic treatment.

However, this approach does not address the economic issue, since the major cost involved in treatment of neutropenic fever is that incurred for in-patient care. Therefore, Malik *et al.*[19] compared out-patient treatment with an oral antibiotic (ofloxacin) to in-patient oral treatment with this same antibiotic, again in patients experiencing neutropenia of short duration. A consider-

able proportion (21%) of their subjects receiving oral antibiotic treatment as out-patients required re-hospitalization and this group had a 4% mortality rate, raising concerns about the safety of this approach.

Most complications associated with neutropenic fever occur during the first few days of each episode. To date, no single risk stratification model has proven successful in the identification of such patients who may be treated safely at home with oral antibiotics, in particular in the case of patients with hematologic malignancies. Therefore, a safer approach might involve early stabilization of low-risk febrile neutropenic patients with intravenous antibiotic treatment in hospital, followed by early discharge of carefully selected patients with subsequent oral antibiotic therapy. This treatment strategy provides time for a proper assessment of a patient's clinical condition, thereby making it possible to exclude patients with infections that are not expected to respond to oral antibiotic treatment and to reduce the potential risk for life-threatening complications occurring outside the hospital. At the same time, this approach enables oral therapy to be individually tailored to the patient's clinical signs and investigation results and minimize the need for extensive monitoring of out-patients.

Here, we combined the MASCC risk-index score with easily attainable clinical and microbiological information concerning the appropriateness of oral antibiotic therapy. Twenty-four hours after defervescence a total of 67 low-risk patients (64%) could be discharged early from the hospital with oral antibiotic treatment. Only three of these patients needed to be re-admitted and two of these readmissions were due to fungal infections that developed more than 7 days after defervescence, and were thus probably unrelated to the antibiotic treatment. This low rate of re-admission, together with the low toxicity of the oral treatment and the absence of mortality due to infection in the out-patients, confirm the safety and feasibility of this treatment strategy.

Overall clinical assessment led to the decision that 36% of the patients classified as low-risk were ineligible for oral antibiotic therapy. Furthermore, these patients exhibited a high incidence of other characteristics associated with poor prognosis, e.g., bacteremia and neutropenia of long duration. One patient in this subgroup remained febrile and died from infection, emphasizing the necessity for initial in-hospital assessment and careful selection of low-risk patients to be discharged with oral antibiotic treatment. The type of underlying malignancy did not have a significant impact on the outcome, as long as the MASCC criteria were strictly applied. However, among the low-risk patients the incidence of acute leukemia was significantly higher among those who were ineligible for oral antibiotic therapy than among those who did get oral therapy. This indicates that underlying malignancy still plays a role in defining the clinical course of the febrile illness. A major advantage of early hospital discharge with oral antibiotic treatment is the improved satisfaction with their care and quality of life experienced by these subjects. Indeed, the majority of these patients were satisfied with this approach to treatment. Moreover, the fact that only one patient was unwilling to be discharged with oral antibiotic treatment may be taken as an indicator of good patient acceptance.

The cost of in-patient care accounts for more than two-thirds of the total cost of treatment in the hospital.[30,31] In the present investigation the mean duration of hospitalization of low-risk patients subsequently treated with oral antibiotics on an out-patient basis was 2.2 days less than that of the corresponding patients treated with conventional approaches. In addition, the saving provided by this strategy may be even greater for other types of patients with febrile neutropenia, e.g., patients being treated for solid tumors, in whom the proportion of low-risk patients is higher.

In conclusion, we have demonstrated that the MASCC risk-index is a valuable aid in the initial identification of patients suffering from hematologic malignancies who run a low risk for complications in connection with febrile neutropenia. Early discharge from the hospital 24 hours after defervescence and subsequent oral treatment with antibiotics was shown to offer a safe and cost-effective alternative to the conventional management of such low-risk patients, provided that relevant clinical and/or microbiological information did not indicate that such oral therapy was inappropriate

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