HOSPITAL CHRONICLES 2007, 2(2): 66–73

REVIEW

Risk Assessment in Adult Cancer Patients with Febrile Neutropenia: A Review of Methods and of Risk-adapted Empiric Treatments

M. Paesmans[1], J. Klastersky[2]

[1]*Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*
[2]*PSOM, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

KEY WORDS: *Febrile neutropenia, Risk assessment, Complication, Risk-adapted therapy*

Address for correspondence:
Marianne Paesmans
Data Centre
Institut Jules Bordet
Rue Héger-Bordet, 1
B 1000 Bruxelles Belgique

Submitted: 16-07-07,
Revised: 18-08-07,
Accepted: 03-09-07

ABSTRACT

Febrile neutropenia is a common complication of antineoplasic chemotherapy. It is a potentially serious event, sometimes lethal. However, it is well recognized that the population of patients with febrile neutropenia is heterogeneous in terms of prognosis. Simplified therapy, for instance oral antibiotic empiric treatment or ambulatory treatment, in comparison to the classical management of intravenously administered empiric antibiotics and in-hospital surveillance, has been the purpose of research for patients predicted at low-risk for serious complications development. However, for such a strategy to be successful an accurate identification of patients at low-risk is required. The objective of the present review is to present the available tools for risk assessment, in adult patients populations and to review the status of our knowledge regarding the efficacy and the safety of risk-adapted therapy.

INTRODUCTION

Febrile neutropenia in cancer patients is a common complication of antineoplasic chemotherapy. It is a potentially serious event, sometimes lethal, although many patients respond quickly to broad spectrum empiric treatment with an indolent course of the febrile neutropenic episode. However, others will develop severe complications and 2% to 10% will even die before resolution of the episode. Febrile neutropenia is also associated with added morbidity, represents increased costs of anticancer treatments and can jeopardize patients quality of life.

Some preventive measures, like the use of colony-stimulating factors, may be effective, but due to cost-effectiveness issues, have to be restricted to selected patients at high risk of developing severe neutropenia and/or febrile neutropenia [1,2]. The use of prophylactic antibiotics is controversial because it may induce emergence of resistant pathogens and does not have any clear impact on mortality [3].

The classical approach at the onset of febrile neutropenia, has been to start empiric broad-spectrum treatment given in a hospital environment [4]. However, as fever and neutropenia resolve quite quickly in many patients without any further complication, it has been recognized, for more than two decades, that febrile neutropenia is quite a heterogeneous syndrome leading to the need to be able to identify the patients who will go well and recover quickly following the administration of the empiric treatment.

Provided we are able to distinguish at least two populations of patients, one at low-risk and one at high-risk, it is possible to look at simplified therapeutic management of low-risk patients. In this review, we will then try to answer the following two questions: a) What are the available tools for identifying low-risk patients ? b) How can therapy be safely adapted and simplified for low-risk patients? As populations of adult patients and children are studied separately for such obvious reasons as differences in underlying disease, in etiology of infections and of type of complications susceptible to occur, we will restrict our presentation to populations of adult patients.

WHAT ARE THE AVAILABLE TOOLS FOR IDENTIFYING LOW-RISK PATIENTS?

Essentially, two approaches are available for selecting a population of patients at low-risk. The first one is to rely on a set of predictive factors published in the literature or chosen on the basis of clinical expertise without analyzing the interaction between them but rather combining them empirically. The advantage of this approach is that the definition of low-risk may be changed very easily depending on the context of use and on the occurrence of new studies' results. The disadvantage is that it is very difficult to assess the performance of the definition in terms of sensitivity, specificity and positive and negative predictive values. The following factors are often considered to delineate low-risk: absence of hemodynamic instability, absence of hypotension, no altered mental status, no respiratory failure, no renal failure, no abnormal hepatic tests, good clinical condition, an expected short duration of neutropenia, no acute leukaemia, no bone marrow or peripheral blood stem cell transplant, absence of chills, no abnormal chest X-ray, no cellulitis or signs of focal infection, no catheter-related infection, no need for intravenous supportive therapy [5-9]. This was the most frequently adopted methodology for the clinical trials which tested oral antibiotic regimens as an alternative for patients considered at low-risk.

The second, more recent approach is to try to develop validated models integrating several factors in a well-defined way and considering their independent value or their interactions. Models have first to be developed and then tested on a separate patients population in order to be certain that they are well calibrated (predicted outcomes have to match observed outcomes) and reliably transportable in other settings (to other institutions for instance); alternatively, cross-validation techniques may be used. Their discrimination ability also has to be regularly monitored. Advantages are that such an assessment of low-risk is standardized and more objective and that the classification has known properties. The method is also more parsimonious with the use of independent only predictive factors. The predicted outcome is also more carefully defined. However, the development process is long; the need for validation should not be underestimated and the context of use has to be considered before introducing them in clinical practice.

To our knowledge, for populations of adult patients, two scoring systems have been developed and validated: the Talcott model and the MASCC score. Both use the same endpoint: the occurrence of serious medical complications (and not the response to empiric treatment). The choice of this endpoint was stressed as a progress in the discussion of risk assessment [10] although the definition of a serious medical complication, presented in Table 1, may appear somehow arbitrary. Indeed, the need to change empiric treatment does not necessarily mean that the clinical course of the patient will not be benign and is felt as less adequate in estimating the risk associated to groups of patients.

THE TALCOTT MODEL :

Talcott and colleagues were the first to define a classification of patients into four groups (Table 2), the so-called group IV (patients out of the hospital at fever onset, with cancer con-

TABLE 1. Medical complications considered as serious as defined in [13]

• Hypotension (defined as systolic blood pressure <90 mm Hg or the need for pressor support to maintain blood pressure)
• Respiratory failure (defined as arterial oxygen pressure less than 60 mm Hg while breathing room air or need for mechanical ventilation
• Intensive care unit admission
• Disseminated intravascular coagulation
• Confusion or altered mental state
• Congestive cardiac failure seen on chest X-ray and requiring treatment
• Bleeding severe enough to require transfusion
• Arrhythmia or ECG changes requiring treatment
• Renal failure requiring investigation and/or treatment with intravenous fluids, dialysis or any other intervention
• Other complication judged serious and clinically significant by the investigator

TABLE 2. The Talcott's classification

Group I	Inpatients (at the time of fever onset)
Group II	Outpatients with acute comorbidity requiring by itself hospitalisation
Group III	Outpatients without comorbidity but with uncontrolled cancer
Group IV	Outpatients with cancer controlled and without comorbidity

Comment: Groupe IV is considered to be at low-risk, there is no constructed ordering for groups I to III.

trolled and without comorbidity) was considered as a low-risk group [11]. Groups were constructed using clinical arguments and expertise and, at a first stage, tested on a retrospective series of 261 patients from a single institution. It was further validated on a prospective series of 444 patients managed at two institutions [12].

THE MASCC SCORE:

The second model was developed thanks to an international prospective study conducted by the Multinational Association for Supportive Care in Cancer (MASCC) [13]. The study population was divided into two parts: one for derivation of the score, the so-called MASCC score based on multivariate logistic regression models (n=756) and one for validating it (n=383). A numeric risk-index score was constructed weighting seven independent characteristics shown to be associated with a higher probability of favourable outcome. The score is presented in Table 3; it ranges from 0 to 26 and a score higher or equal to 21 was defined as predicting low-risk for complication. This threshold was chosen targeting, in the derivation set, a rate of complications of 5%, as a compromise between positive predictive value and sensitivity of the clinical prediction rule. The characteristics of both models, Talcott's and MASCC, on the validation set used in Klastersky[13] are shown in Table 4. So, Klastersky's publication [13] can be seen as a further validation of the Talcott score. Comparing the characteristics of the prediction rules, the MASCC score constituted an improvement of the sensitivity and of the overall misclassification rate. On the other hand, the positive predictive value might be lower, at least when the threshold of 21 is used. Increasing the threshold might be a way to increase positive predictive value but will also reduce the improvement in the sensitivity of the model.

The MASCC score was then validated on new series. Uys et al [14] studied prospectively 80 episodes of febrile neutropenia, occurring mostly in patients with solid tumor; 58 of them were classified as low-risk (score ≥21), only 1 developing a serious complication. Twenty-two episodes were considered as high-risk. Although 11 patients recovered without complication, 8 deaths were observed in that subgroup.

A second multicentric study, initiated by the MASCC study section on infectious diseases, also prospectively validated the score, although more than half of the patients were registered by a single institution. One thousand and three first eligible episodes were studied [15], 549 occurring in patients with haematological tumor and 454 in solid tumor patients. Overall, 72% of the episodes were classified as low-risk with a positive predictive value of 88% (for a sensitivity of 79% and a misclassification rate of 26%). In solid tumor patients, positive predictive value was 93% while it was decreased to 84% in haematological malignancies. We should emphasize that the underlying disease is not integrated in the score although it can be considered as a surrogate for neutropenia duration. Some further research might be specially indicated in haematological malignancies and the lower positive predictive value in that subgroup might be an issue when using the score as an element of the therapeutic decision, as will be discussed later. That scoring system is presently recommended by the IDSA guidelines as a valuable tool for identifying low-risk patients [4].

Other endpoints have been considered, namely bacteremia or serious (also named invasive or significant) bacterial infection [10], most often in populations of children which are not the focus of the present review. By doing so, the outcome is chosen as a surrogate of an infection susceptible to lead more frequently to adverse outcome. The adequacy of that endpoint might be different in children and in adults. One disadvantage is that some documented infections might be no

TABLE 3. The MASCC risk-index

Characteristic	Weight
Burden of illness (ie febrile neutropenia):	
no or mild symptoms	5
moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age <60 years	2

The score is obtained by summing up the different weights (the weights for burden of illness are not cumulative) and ranges from 0 to 26. Patients with a score ≥21 are considered at low-risk.

TABLE 4. Characteristics of the clinical prediction rules derived from Talcott's and MASCC classifications – Validation set from [13] (n=383 patients)

Group	Sensitivity	Specificity	PPV	NPV	Miscl
Talcott's group IV	0.30	0.90	0.93	0.23	0.59
MASCC ≥21	0.71	0.68	0.91	0.36	0.30

PPV=positive predictive value; NPV=negative predictive value

more associated with complications than fevers of unknown origin; furthermore, the impact of identifying patients at risk for such an endpoint may not have as direct implications on the management of the patients as does the prediction of the occurrence of a serious medical complication [10].

HOW CAN THERAPY BE ADAPTED AND SIMPLIFIED FOR LOW-RISK PATIENTS?

Several approaches can be considered as alternatives to the classical approach (hospitalisation and intravenous broad-spectrum empiric antibiotic treatment) with two key elements: oral antibiotics and outpatient treatment. Simplified management can then include early shift from intravenous therapy to oral therapy, upfront oral therapy, early discharge under intravenous or oral therapy or full outpatient management.

ORAL TREATMENT OR EARLY SWITCH FROM INTRAVENOUS TO ORAL TREATMENT

The feasibility of oral therapy has been extensively studied. Already in 1991, French investigators studied self-administration of oral pefloxacin/amoxicillin-clavulanic acid in 68 febrile episodes occurring after chemotherapy in lymphoma outpatients. Although one death was observed, there was no need for hospitalisation in more than 80% of the episodes [16]. After that study, which, however, directly evaluated oral treatment in outpatients without any intermediate step, there were several randomised studies addressing the issue of the success rate of oral treatment (sometimes with short intravenous therapy preceding a switch to oral) compared to that of intravenous treatment. Indeed, we believe that the question of efficacy of an oral regimen is something different than the possibility to treat patients as outpatients. Eligibility criteria for oral therapy are somewhat different than those that can be considered for ambulatory management. In the second situation, many aspects have to be taken into account including psychosocial conditions and home environment in addition to classical criteria allowing for an oral medication (no nausea and no vomiting, ability to swallow, ...). These various trials looking at efficacy of oral treatment were reviewed in a meta-analysis [7]. Fifteen trials were included in the systematic review, and all based their assessment of low-risk on clinical criteria. In ten trials, the oral arm was a pure one while in 5, a sequential approach (intravenous followed by oral) was used. The oral treatment consisted of a quinolone only in 6 trials, a quinolone in combination with another oral agent in 7 and of cefexime in 2. The aggregation of the results led to the conclusion that the response rate to oral therapy is as good as the one obtained with intravenous treatment with a relative risk for treatment failure of 0.96 (95% CI from 0.84 to 1.11) in favour of the oral arm. Observed mortality was also lower with the oral regimen, with a relative risk of 0.83 (95% CI: 0.49-1.40). However, although the conclusion about efficacy is somewhat straightforward and accurate enough to be convincing, the confidence intervals remain large for mortality and it is not legitimate to conclude that there is no difference.,Nevertheless, with the present accumulation of data, there is no reason to have concerns about mortality.

The main message from the trials as well as from the reviews and meta-analysis is that oral treatment is a safe alternative in selected low-risk patients although we do not know from these reports how to optimally select low-risk patients as there was heterogeneity in the selection criteria.

OUTPATIENT TREATMENT

This issue is much more critical and has been less extensively studied and less often by using a randomised design. Although some investigators at the MD Anderson Cancer Center have acquired a long and successful experience of outpatient management [17,18], many authors [19,20] expressed the opinion, at the time oral treatment was convincingly shown as effective, that oral treatment and ambulatory management are two very different issues and that careful assessment of risk but also of patients' other conditions (like compliance to treatment and home environment) has to be made before sending a patient back home together with an adequate and efficient algorithm for monitoring the patient once he is at home. This last point appears to us very important as the possibility for adequately monitoring a patient outside of hospital may be varying in different types of institutions. Below we will review some studies having addressed the question of oral therapy in an outpatient setting.

In 1994, Talcott published a pilot study of home therapy (after two days in hospital) for patients, using his validated prediction rule as a guide for therapeutic management. This trial was intended to be a preliminary step before a randomised study. However, out of the 30 patients, admission was required in 9 (30%), a rate that must be considered as too high even if not all patients readmitted developed a serious complication [21]. The subsequent randomised study suffered from some difficulties in accrual but the situation appears to be improved [22]. In 1995, Malik et al [23] reported the results on 182 febrile neutropenic episodes considered at low-risk (although some occurred in acute leukaemic patients, a fact which might not be acceptable by all) randomised between an oral outpatient treatment versus an in-hospital intravenous treatment. Response rates were similar in the two arms but, in the patients treated at home, the need for hospitalisation was 21% with a mortality rate of 4%, leading to some concerns about the safety of the approach. We already mentioned the experience from the MD Anderson Cancer Center using both intravenous and oral regimens in the outpatient setting with satisfactory success rates and low need for hospitalisation. The last published experience from that institution was in 2006 [24] and addressed, in a pilot study, the feasibility of using an empiric, oral outpatient quinolone monotherapy, gatifloxacin. As the authors noted, the MASCC score was not yet published at the time

they designed the study and they used the Talcott criteria for defining low-risk. They also restricted the underlying disease to breast cancer or sarcoma as in their experience, these two types of tumors constitute more than 90% of their low-risk criteria. To further reduce the risk, they excluded patients with any focus of infection or impaired renal/hepatic functions. Regarding the eligibility of the patient to be treated with gatifloxacin, they required no known allergy to any fluoroquinolone and the absence of mucositis of grade ≥2. Fourty patients were included (36 had low-risk prediction by the MASCC score). Thirty-eight patients responded to gatifloxacin (95% with a 95% CI from 83% to 99%) and thirty-seven responded to outpatient therapy (92%, 95% CI from 80% to 98%). One of the three patients requiring hospital admission had a MASCC score ≥21. More recently, a randomised comparison was performed by Innes et al [25] in a single institution. The definition of low-risk was inspired from the Talcott model but the authors added extra criteria (like an underlying cancer being a solid tumor or a lymphoma or an anticipated short duration of neutropenia). The MASCC score was not available at the time the study was designed; a retrospective assessment led to the conclusion that more than 95% of the included episodes were associated with a MASCC score ≥21 but it can be anticipated that the study population was a restricted group of patients with a score ≥21 due to the expected larger sensitivity of the MASCC score. One hundred and twenty-six episodes (occurring in 102 patients) were randomised between in-hospital intravenous treatment with gentamicin and tazocin compared to an oral regimen with ciprofloxacin and amoxicillin-clavulanate and discharge as early as possible after 24 hours of hospitalisation. In the orally treated 66 episodes, the rate of discharge after 2 days was 55%. In both arms, the therapeutic results were excellent with the development of only one serious complication in each arm. From the economic perspective, the prospectively planned cost analysis revealed a reduction in the costs from a mean of £840 to £470. The mean nursing hours were also reduced (from 21 hours to 11 hours). The authors concluded that the oral treatment combined with the early discharge was a safe cost-effective alternative to conventional management but stressed that the results of the approach might be different when used outside a single specialist center and they argue about the necessity of conducting a larger multicentric trial. A survey performed by the same team among UK physicians showed that there was only little introduction of newer strategies for the management of low-risk febrile neutropenia, but that the willingness to perform that large study was high [26]. In other countries, there can be a larger introduction of adapted therapy according to risk assessment. A single institution study testing oral treatment (also ciprofloxacin and amoxicillin-clavulanate) and discharge following 24 hours of in-hospital surveillance was conducted in one of the institutions having derived the MASCC score and using it as a tool for defining low-risk [27]. Low-risk prediction was, however, complemented by additional criteria (some of them to assess suitability of oral treatment with ciprofloxacin and amoxicillin-clavulanate: absence of antibiotic prophylaxis, absence of nausea and vomiting and others to assess psychosocial conditions and home environment). Early discharge was allowed whenever possible but was not required by the protocol. All febrile neutropenic episodes were screened, 611 during the study period, 441 predicted at low-risk and 189 eligible for oral therapy (main reason of exclusion was administration of prophylactic fluoroquinolones, most often to patients with haematological malignancies) in 178 patients. The 178 first episodes constituted the group studied for the primary analysis. Seventy-nine patients (44%) benefited from early discharge, three had to be readmitted but none of them presented a serious complication. The overall strategy success was then 95% (95% CI: 92%-100%). Among the 99 remaining patients, 9 developed a serious medical complication including 2 patients who died before resolution of the episode; the overall rate of resolution without serious complication was 91% (95% CI: 85%-97%), with an improved rate of 96% when no clear medical reason for prolonged hospitalisation was present whereas it was only 79% in the reverse situation. This study showed that adapted treatment is feasible for predicted low-risk patients on the basis of the MASCC score. However, low-risk prediction and suitability for oral ambulatory treatment are different issues and the proportion of patients fully benefited from the adapted approach can not be considered very high leading to the conclusion that more efforts are needed to identify the right patients suitable for home therapy. In any case, it was possible to manage a subgroup of patients under conditions of reduced cost and probably improving the patients quality of life. Another recently published study [28] tested the usefulness of the MASCC score with a similar design but included only patients with haematological malignancies. The objective of the trial was to study the feasibility and safety of early discharge of low-risk patients 24 hours after defervescence with a switch from intravenous to oral therapy. They followed 279 episodes of febrile neutropenia in 191 patients, 105 (38%) predicted by the MASCC score as low-risk and 174 as high-risk; about half of these episodes occurred in patients with acute leukaemia and another 30% in non Hodgkin's lymphoma patients. Serious medical complications occurred in 63% of high-risk episodes and 15% of low-risk episodes ($p<0.0001$) for an overall misclassification of 28%; modifications of the initial antibiotic therapy were required more often in patients predicted as high-risk. This validates the discriminant value of the score at a threshold of 21 but also confirms its lower positive predictive value in haematological patients (85%). Among the predicted as low-risk patients, 38 were ineligible for a switch to oral therapy, for various reasons, including documentation of infection, clinical deterioration, swallowing problems or in a few cases

(5), due to a reason not strictly linked to the infectious process. All other low-risk patients were switched to oral therapy 24 hours after defervescence and they were discharged home with oral treatment to be continued for 5 days. No mortality was observed in these discharged patients although 2 patients required readmission (one 2 days after discharge for fever recurrence and another much later due to development of fungal infection). The authors felt that the score was a useful tool for identifying low-risk haematological malignancies combined with initial intravenous therapy and in-hospital surveillance. They applied it in multiple episodes for the same patients even though no change was observed in their conclusions when restricting the analysis on the first episodes only. Thirty-six patients who were treated with oral antibiotic therapy were asked to answer to a questionnaire of satisfaction and 94% stated their preference for oral antibiotic therapy in case of future low-risk febrile episode. In another, quite recent, study [29], the authors included 55 MASCC low-risk episodes (score ≥21) occurring in 54 patients whom they treated with oral moxifloxacin and G-CSF immediately in an outpatient setting. Additional criteria were used, related to patients' ability to take oral medication or to the risk of complication (patients with acute leukaemia, transplant, chronic obstructive pulmonary disease, documented pneumonia, hypotension, signs of dehydration, elevated creatinine level or transaminases level were excluded). Treatment was successful in 50 episodes (91%); 5 hospital admissions were required although only 1 patient developed a serious complication (septic shock due to a staphylococcus infection). No patient died while on the study. Another study with a larger sample size was conducted by the EORTC Infectious Diseases Group testing the effectiveness of moxifloxacin in low-risk febrile neutropenic patients who were selected using the MASCC score. The comparison arm consisted of ciprofloxacin and amoxicillin-clavulanate. Outpatient treatment and/or early discharge was planned in the protocol if additional criteria were met and one of the objectives of the study was to estimate under general conditions and in the context of a multicentric, multinational study, the proportion of patients with successful early discharge. Its findings are currently under analysis. An Italian study, from University La Sapienza in Rome, was performed in outpatients treated for an haematological malignancy. Patients were instructed to attend the haematological emergency unit, in case of fever development. Their MASCC score was assessed and their management was organized according to a prediction of low-risk (score ≥21) or high-risk. All patients started on empiric treatment with intravenous ceftriaxone and amikacin. High-risk patients were managed fully in-hospital. Low-risk patients were planned to be discharged on oral cefixime (or parenteral antibiotics or another oral therapy in case of failure of empiric regimen), after defervescence for 48 hours and in the absence of deterioration of clinical status, regardless of their neutropenic status One hundred consecutive episodes (87 outpatients) were included in the study, 90 with a low-risk prediction and 10 with a high-risk prediction. In thirty-one episodes, the patients were not eligible for early discharge, because of prediction as high-risk at admission, clinical deterioration or patients' refusal. In sixty-nine episodes, all with a baseline low-risk prediction, the patients were discharged on oral cefixime (54 cases), on the initial parenteral regimen (14 cases) or on oral levofloxacin (1 case). Two readmissions were required but no serious complications occurred. Once again, the authors stressed that risk prediction is a different issue from safe outpatient management and they believe this concept is particularly true in patients with haematological malignancies.

CONCLUDING DISCUSSION

There is no doubt that febrile neutropenia is a heterogeneous condition and that any accurate risk stratification system is a valuable tool in guiding the management of selected groups of patients. Furthermore, there are evidence-based data and reviews showing that oral treatment is a safe and feasible alternative to conventional intravenous therapy and the published scoring systems for predicting risk are sufficiently validated to guide patient selection for administration of oral treatment; in such cases a scoring system is adopted; the MASCC score should probably be preferred because of increased sensitivity at a low cost to positive predictive value. However, there is still room for improvement, especially in the population of patients with haematological malignancies. Further research should be conducted, particularly in the field of rapid laboratory tests [10] as most of the clinical data have been already studied and as the inclusion of variables considered to be associated to the duration of neutropenia (like the chemotherapy drugs, the interval from chemotherapy and onset of fever, ...) failed to improve the discriminant value of the MASCC scoring system [30]. The issue of ambulatory treatment is more delicate; indeed, the studies had more varying designs in terms of timing of discharge and we have few data from randomised studies. From most of the published reports, however, it can be concluded that an initial surveillance in-hospital might be extremely important for the safety of the management. In that context, the scoring systems remain a valuable tool but with additional criteria, at least those not linked to risk but related to patients' expected compliance to treatment and to monitoring measures as well as to home environment. The acceptable range of positive predictive values of scoring systems should probably be more restricted or additional criteria plausibly associated to risk might be considered. Further research should also be conducted looking at variables predictive of outcome but collected in the short term follow-up. Indeed, the usefulness of reassessment of the currently available scoring systems has not been sufficiently studied. They are probably

of marginal value as most of the variables included in them are not susceptible to change. Ambulatory oral treatment has been shown to be very effective and safe in strictly selected groups of patients compared to the total population of those predicted at low-risk. Increasing the ratio between patients predicted at low-risk and those effectively and safely discharged would certainly be the goal of further research.

REFERENCES

1. Aapro MS, Cameron DA, Pettengell R, Bohlius J, et al. EORTC guidelines for the use of colony-stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006; 42:2433-2453.
2. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, et al. 2006 Update of Recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; 24:3187-3205.
3. Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention and treatment. *Lancet Oncol* 2003; 4:595-604.
4. Hughes WT, Amstrong D, Bodey GP, Bow EJ, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34:730-751.
5. Freifeld A, Marchigiani D, Walsh T, Chanock S, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during chemotherapy. *New Engl J Med* 1999; 341:305-311.
6. Kern WV, Cometta A, De Bock R, Langenaeken J, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *New Engl J Med* 1999; 341:312-318.
7. Vidal L, Paul M, Ben dor I, Soares-Weiser K, et al Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. *JAC* 2004; 54:29-37.
8. Paesmans M. Risk factors assessment in febrile neutropenia. *Int J Antimic Agents* 2000; 16:107-111.
9. Klastersky J, Paesmans M. Risk-adapted strategy for the management of febrile neutropenia in cancer patients. Support Care Cancer 2007; Electronic publication, February 9.
10. Kern WV. Risk assessment and treatment of low-risk patients with febrile neutropenia. *Clin Infect Dis* 2006; 42:533-540.
11. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of patients with fever and neutropenia: clinical identification of a low-risk subgroup at presentation. *Arch Intern Med* 1988; 148:2561-2568.
12. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992; 10:316-322.
13. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; 18:3038:3051.
14. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multniational Association for Supportive Care in Cancer (MASCC) risk-index score. *Supp Care Cancer* 2004; 12:555-560.
15. Paesmans M for the MASCC Study Section on Infections. The duration of febrile neutropenia. 8th International Symposium on Febrile Neutropenia, Athens, Greece, January 2006.
16. Gardembas-Pain M, Desablens B, Sensebe L, Lamy T, et al. Home treatment of febrile neutropenia: an empirical oral antibiotic treatment. *Ann Oncol* 1991; 2:485-7.
17. Rubenstein EB, Rolston K, Benjamin RS, Loewy J, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* 1993; 71:3640-3646.
18. Rolston K, Rubenstein E, Elting L, Escalante C, et al. Ambulatory management of febrile episodes in low-risk neutropenic patients (abstract LM 81). *In:* Program and Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology (Washington DC), 2005.
19. Finberg RW, Talcott JA. Fever and neutropenia: how to use a new treatment strategy. *N Engl J Med* 1999; 341:362-362.
20. Feld R, Paesmans M, Freifeld AG, Klastersky J, et al. Methodology for clinical trials involving patients with cancer who have febrile neutropenia: updated guidelines of the Immunocompromised Host Society/Multinational Association for Supportive Care in Cancer, with emphasis on outpatient studies. *Clin Infect Dis* 2002; 35:1463-1468.
21. Talcott JA, Whalen A, Clark J, Rieker PP, et al. Home antibiotic-therapy for low-risk cancer-patients with fever and neutropenia - A pilot-study of 30 patients based on a validated prediction rule. *J Clin Oncol* 19994; 12:107-114.
22. Talcott JA, Yeap B, Godley PA, Lu C, et al. Does home antibiotic therapy increase medical risk for patients with low-risk febrile neutropenia? A multi-institutional randomized trial (abstract 8113). In: Proceedings of the 2004 American Society of Clinical Oncology Annual Meeting. *J Clin Oncol* 2004; 22:8113.
23. Malik IA, Khan WA, Karim M, Aziz Z, et al. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. *Am J Med* 1995; 98:224-231.
24. Rolston KVI, Manzullo EF, Elting LS, Frisbee-Hume SE, et al. Once daily, oral, outpatient quinolone monotherapy for low-risk cancer patients with fever and neutropenia. A pilot study for low-risk cancer patients with fever and neutropenia. *Cancer* 2006; 106:2489-2494.
25. Innes HE, Smith DB, O'Reilly SM, Clark PI, et al. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. *Br J Cancer* 2003; 89:43-49.
26. Innes H, Billingham L, Gaunt C, Steven N, et al. Management of febrile neutropenia in the United Kingdom: time for a national trial? *Br J Cancer* 2005; 93:1324-1328.
27. Klastersky J, Paesmans M, Georgala A, Muanza F, et al. Management with oral antibiotics in an outpatient setting of febrile

neutropenic cancer patients selected on the basis of a score predictive for complications. *J Clin Oncol* 2006; 24:4129-4134.

28. Cherif H, Johansson E, Bjφrkholm M, Kalin M. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. *Haematologica* 2006; 91(2):215-222.
29. Chamilos G, Bamias A, Efstathiou E, Zorzou PM, et al. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. *Cancer* 2005; 103:2629-2635.
30. Paesmans M for the MASCC Study Section on Infectious Diseases; The duration of febrile neutropenia. Abstract presented at the 8th International Symposium on Febrile Neutropenia, Athens, Greece, January 2006.