Chapter 4

Management of the low-risk patients

Orally administered antimicrobial therapy

The Multinational Association of Supportive Cancer Care (MASCC) score index has been developed to predict a low risk (<5%) of complications in patients with febrile neutropenia (FN). In our original study, a score ≤21 identified low-risk patients with a positive predictive value of 91%, specificity of 68%, and sensitivity of 71% [1]; these patients had <5% of severe complications and 16% died (4 out of 243). More recent validations of the MASCC score have confirmed a somewhat higher frequency of complications (12–18%), but still a low mortality of 2–3% [2,3].

The paradigm of antimicrobial therapy for FN has been the intravenous administration broad spectrum antibiotics, either as combinations or single-drug therapy with extended spectrum agents [4]. This has been challenged by studies showing that in low-risk patients oral therapy with ciprofloxacin plus amoxicillin clavulanate was as effective as intravenous therapy [5]. More recently, oral moxifloxacin was demonstrated as efficacious as oral combination therapy in patients at low risk of infection during FN [6], which makes a schedule of a once daily administered oral antimicrobial therapy feasible [7].

Of course, there are limitations for the use of oral antimicrobial therapy; in a large study validating the concept of oral antibiotics for patients with FN and using the MASCC score for predicting a low risk of infection, we found that there were several reasons for not administering oral treatment to such patients [8]. As summarized in Table 4.1, these

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Reasons for not administering oral treatment to patients predicted at low risk of serious complication development

Reason	No. of patients	%
Antibacterial prophylaxis and/or treatment	179	71
Inability to swallow	27	11
Contraindication(s) to oral therapy	17	6
Protocol violation	16	6
Refusal (by patient or physician)	11	5
Allergy to penicillin or quinolones	2	1

Table 4.1 Reasons for not administering oral treatment to patients predicted at low risk of serious complication development. Multinational Association for Supportive Care in Cancer score of ≥21. Reproduced with permission from © American Society of Clinical Oncology 2013, Klastersky et al [8]. All Rights Reserved.

were anterior antibacterial prophylaxis and/or treatment (71%), inability to swallow, other contraindications to oral therapy, refusal by the patient, or allergy to the proposed drugs [8]. In such cases, the intravenous administration of antibiotics is mandatory, although it does not preclude necessarily outpatient therapy [9].

On the other hand, the oral administration of antibiotics to patients with FN can be safely performed in hospitalized patients as shown in the initial studies testing the hypothesis of an effective oral antimicrobial therapy for low-risk patients with FN [5,10], with a potential for providing more comfort to the patients and for reducing the overall cost of management.

Fluoroquinolones have been the corner stone of orally administered antimicrobial therapy for low-risk patients with FN [5–7,10]. Of course, the major caveat with the use of fluoroquinolones for therapy is the potential emergence of resistant strains. The emergence of fluoroquinolone-resistant bacteria, namely *Escherichia coli*, in patients receiving fluoroquinolones as a prophylaxis for FN had been reported in the mid 1990s [11]; at that time, it was noted that these fluoroquinolone-resistant strains were also cross-resistant for all quinolones and multiresistant for a series of antibiotics, including trimethoprim-sulfamethoxazole, ampicillin, doxycycline, and others. The epidemiology of these fluoroquinolone-resistant *E. coli* can be altered by the antibiotic policy at a given center: a 6-month fluoroquinolone prophylaxis discontinuation decreased the incidence of

resistant *E. coli* from >50% to 15%, but at the same time the incidence of Gram-negative bacteremia increased from 8% to 20%; the resumption of prophylaxis decreased the incidence of bacteremia and increased the frequency of resistant isolates to preintervention levels [12]. In another study on the epidemiological changes and emergence of resistance to fluoroquinolones in patients with hematological malignancies, 40% of those who were receiving prophylaxis with levofloxacin, isolation of resistant *E. coli* was independently associated with prophylaxis and duration (>7 days) of neutropenia [13]. In that study, there was a reduction of the incidence of FN with the use of levofloxacin prophylaxis and the infections caused by resistant strains did not show a worse outcome. However, in another study, patients with resistant strains (*E. coli* and *Klebsiella pneumoniae*) were significantly less likely to receive empirical therapy with activity against the offending pathogen, as a result of emergence of multiresistant bacteria [14]. The observation that these fluoroquinolone-resistant strains can be multiresistant is a major concern. For all these reasons, the extensive use of fluoroquinolones for prophylaxis of infection should be discouraged, as it reduces the availability of quinolones for oral therapy of FN [8], and more importantly might make these important antimicrobials globally useless.

Early hospital discharge

Although there are potential disadvantages with early hospital discharge (eg, the risk of noncompliance or limited supervision) for low-risk patients with FN, overall there are many positive aspects, including enhanced quality of life for the patients and lowered costs of care (Table 4.2) [15].

Innes et al [16] published a first prospective randomized comparative study between the standard approach (intravenous antibiotics in an inpatient setting) and a combination of oral therapy in outpatients. The latter approach was not inferior in terms of efficacy and resulted in an estimated 50% cost saving. In that study, the low-risk patients were selected using the Talcott's criteria with additional requirements for the sake of maximal safety, resulting in a very strict definition of "low risk" and thus limiting the eligible population. These authors, nonetheless, confirmed their initial observations in a subsequent study using the MASCC index

Advantages and disadvantages of risk-based therapy outside of the hospital
Advantages
• Avoidance of iatrogenic and other hazards of hospitalization
• Reduced rate of "healthcare associated" infections
• Lower cost of care
• Enhanced quality of life (patients)
• Increased convenience (family)
• More efficient resource utilization
Disadvantages
• Potential for serious complications in an unsupervised setting
• Potential for noncompliance
• Need to maintain an (expensive?) infrastructure

Table 4.2 Advantages and disadvantages of risk-based therapy outside of the hospital. Reproduced with permission from © Taylor and Francis 2013, Rubinstein, Rolston [15]. All Rights Reserved.

score for selecting the low-risk patients [17], and validated its usefulness as a predictive score for a low risk of complications during FN.

Klastersky et al examined a similar strategy using the MASCC index score to define low risk in 611 consecutive patients with FN seen over 3 years at the Institut Jules Bordet [8]. Patients suitable for oral therapy with combination of amoxicillin clavulanate plus ciprofloxacin were eligible for discharge after a minimum 24-hour observation period. Eligible patients (n=178, 44%) were discharged within 2 days; no severe complications were observed and only 3 patients (4%) required readmission. The main reason for not administering oral antibiotics to otherwise low-risk patients was the concomitant use of antibacterial prophylaxis (71%); the main reason for prolonged hospitalization in patients eligible for early discharge was persistent fever, need for treatment change, or other medical complications during the 24-hour observation period; in those patients, the rate of severe medical complication was 9% (Table 4.3) [8].

In a similar study, Cherif et al confirmed the value of the MASCC score for identifying low-risk patients with hematological malignancies [18]. In that series, all patients were started on intravenous antibiotics as inpatients and were transferred to oral therapy if they remained clinically stable and defervesced. There were only 3 (5%) readmissions; the mean hospital stay was 6 days, clearly longer than in the two preceding

Reasons for prolonged hospitalization in predicted low-risk patients receiving oral empiric treatment

Reason	No. of patients
Persistent fever and need for treatment change	19
Objective medical reason	42
Subjective medical reason	10
Reason not related to a medical event	28

Table 4.3 Reasons for prolonged hospitalization in predicted low-risk patients receiving oral empiric treatment. Reproduced with permission from © American Society of Clinical Oncology 2013, Klastersky et al [8]. All Rights Reserved.

studies, which mostly included patients with solid tumors. A similar strategy of a prompt step-down from intravenous to oral therapy was found not inferior to full inpatient management with intravenous antibiotics in children with FN [19].

A meta-analysis of 10 studies comparing inpatient versus outpatient therapy of FN [20] did not find any significant difference in mortality or response rate. The readmission rate for the outpatient was 14% overall, primarily for persistent fever rather than life-threatening complications. That meta-analysis provides strong evidence that outpatient management of FN, in carefully selected patients, is as safe and effective as standard inpatient therapy.

More recently, Teuffel et al published another systematic review and meta-analysis of 14 randomized studies about outpatient management of cancer patients with FN [21]. They concluded that outpatient treatment of FN was a safe and efficacious alternative to inpatient management. The same group analyzed the cost effectiveness of outpatient treatment for FN in adult patients with cancer [22]; they concluded that, for such patients, hospital treatment is more expensive than outpatient strategies. A retrospective study by Elting et al also concluded that outpatient management of low-risk patients with FN was as safe and effective as inpatient management and significantly less costly [23].

Predicting the risk of serious complications during an episode of FN (by using validated tools, such as the MASCC index score) and predicting the safe early discharge from the hospital of a patient with FN on oral antimicrobial therapy remain somewhat different issues. In our study [8], we found that 9% of the patients who were not sent home after a 24-hour

observation within the hospital developed serious complications, despite having been selected as low-risk patients by the MASCC scoring index at the time of their admission. The in-hospital observation is probably very important when selecting those patients suitable for early discharge. Nonetheless, many centers will send low-risk patients back home after a mere 4- to 8-hour observation period, after safely administering the first dose of prescribed antibiotics.

The most crucial approach for most of these patients is further, close monitoring. Patients should be given specific instructions if they feel worse or develop serious symptoms; they should be instructed to immediately seek medical advice or, even better, to return to the hospital. They should be encouraged to record their body temperature several times a day and to list their potential problems.

Those patients should be seen at follow-up clinics regularly and in between (contacted by phone) to review clinical and laboratory data and to make decisions regarding possible response failure, drug toxicity, and other potentially adverse events [24].

Table 4.4 summarizes the issues which will need more research to make orally administered regimens and early discharge for low-risk cancer patients with FN widely acceptable.

It is also possible that information on patients' preferences for outpatient treatment might help to optimize healthcare delivery to low-risk patients with FN. In a recent study [25], the probability of return to the hospital was the most important attribute to patients when considering home-based care for FN.

Remaining issues about the acceptance of orally administered antibiotics and early discharge for low-risk cancer patients with febrile neutropenia
Predictive factors for discharge
Standardized surveillance system
Education of physician and patient anxiety about safety
Demonstration of a quality-of-life benefit
Applicability to low income countries and rural areas
Definition of the cost effectiveness
Patients' preferences

Table 4.4 Remaining issues about the acceptance of orally administered antibiotics and early discharge for low-risk cancer patients with febrile neutropenia.

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