Summary and concluding remarks
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In the Netherlands approximately 7000 patients are diagnosed with a malignancy of the blood or bone marrow every year. Prospects for these patients have substantially improved over the past decades. The field of clinical haematology is characterized by rapid and sometimes exciting innovations in treatment options, achieving higher remission rates and control over diseases that were deemed incurable until recently. The advent of combination chemotherapy, dose intensification, autologous and allogeneic stem cell transplantation and immunotherapy all have contributed substantially to this progress in the treatment of haematological malignant diseases. Unfortunately, these important and promising developments are counterbalanced by serious impairment of host immune response mechanisms. This occurs in a population of patients that is already running a serious risk of infections, because haematological malignancies reside by definition in the immune system itself. As a consequence, these patients are highly susceptible to infections with various kinds of opportunistic pathogens, including viruses, bacteria and fungi.

Infections in patients with aggressive haematological malignancies are associated with significant morbidity and mortality. Moreover, their initial presentation frequently is erratic, with sometimes only minimal signs and symptoms. Therefore, it is not surprising that anti-infective strategies have focused on prevention and early treatment. Antibacterial and antifungal prophylaxis and early, or ‘empirical’ antibiotic therapy have gained a lot of interest in the international literature. In chapter 2 an overview is given on current insights and developments on antibacterial and antifungal prophylaxis and treatment, from a clinical perspective.

In view of the serious consequences of infections in patients treated for haematological disease, it is tempting to clinicians to readily introduce newly marketed and promising antibacterial and antifungal drugs into daily clinical practice, before results of relevant clinical trials have become available. This entails the risk of neglecting important questions considering safety, pharmacokinetic behaviour and efficacy of the drug involved, as prophylaxis or treatment in the specific population of patients with haematological diseases.

The studies described in this thesis aimed to explore the safety and efficacy of a selection of new antimicrobials, for the prevention of bacterial (chapter 3 and 4) and fungal (chapter 5...
Summary and concluding remarks

and 6) infections, as well as for the empirical treatment of bacterial infections (chapter 7). The occurrence of an outbreak of vancomycin-resistant Enterococcus faecium (VRE) led to an assessment of risk factors for the acquisition of VRE and recommendations for the prevention and control of such an outbreak (chapter 8).

Main results

Chapter 3. Gram-positive breakthrough infections pose a major drawback to the use of quinolones for antibacterial prophylaxis in neutropenic patients. Levofloxacin, a relatively new quinolone, has an augmented Gram-positive spectrum and may potentially overcome this problem. When administered orally (500 mg, once daily) as antibacterial prophylaxis to patients receiving intensive chemotherapy for haematological malignancies, levofloxacin provided adequate eradication of Gram-negative microorganisms and S. aureus and preserved the anaerobic component of the bowel flora. It was found that the pharmacokinetic properties of levofloxacin were not altered during the phase of chemotherapy and neutropenia. Minimal inhibitory concentration (MIC) values for viridans group (VG) streptococci tended to increase, which cautioned against the occurrence of acquired resistance to levofloxacin.

Chapter 4. Elaborating the results described in chapter 3, the question remained open as to how levofloxacin prophylaxis compared with standard prophylactic regimens, considering efficacy, tolerability and induction of resistance among bacterial pathogens. In an attempt to answer this question, levofloxacin was compared with ciprofloxacin plus phenethicillin as antibacterial prophylaxis during neutropenia, in a randomized clinical trial. It was found that levofloxacin and ciprofloxacin-phenethicillin were equally effective in the prevention of bacterial infections in neutropenic patients. However, levofloxacin was better tolerated, which may benefit compliance with therapy. In line with the findings described in chapter 3, resistance to levofloxacin was observed among VG streptococci, but timely adjustments of the prophylactic regimen were made, based on surveillance culture data and no break-through infections with VG streptococci occurred.

Chapter 5. In an attempt to improve prophylaxis against the occurrence of invasive fungal infections in neutropenic patients, a randomized clinical trial was designed to compare a lipid formulation of amphotericin B intravenously (amphotericin B colloidal dispersion, ABCD)
Chapter 9

with oral fluconazole. However, the administration of ABCD for prophylactic reasons to patients without life-threatening fungal infections, was associated with major and intolerable side-effects during infusion of the compound. The study was prematurely terminated and it was concluded that ABCD appeared to be unsuitable for antifungal prophylaxis in neutropenic patients.

Chapter 6. It is well documented that administration of itraconazole increases cyclosporin A (CsA) serum concentrations. However, there are no data on the effects of CsA on itraconazole pharmacokinetics. Itraconazole and hydroxy-itraconazole pharmacokinetic parameters were studied, before and during administration of cyclosporin A (CsA) in ten patients receiving an allogeneic stem cell transplantation. It was found that exposure to OH-itraconazole, but not to itraconazole is increased when itraconazole is co-administered with CsA. Monitoring of itraconazole serum concentrations is important in patients who use drugs that, like itraconazole, interact with CYP3A4 and when target drug concentrations are to be achieved for optimal antifungal efficacy.

Chapter 7. With the introduction of cefpirome, a new fourth generation cephalosporin, as empirical treatment of febrile neutropenia, a cohort study was conducted to assess the clinical efficacy of cefpirome and its activity against isolated pathogens. Fifty-three percent of patients survived the neutropenic episode without the need of treatment modification (success-rate 53%). Susceptibility testing of isolated pathogens showed adequate coverage of a broad range of Gram-positive and Gram-negative microorganisms including viridans group streptococci, coagulase-negative staphylococci, Enterobacteriaceae and Pseudomonas aeruginosa. In addition, pharmacokinetic data indicated that a dosing regimen of cefpirome 2 g twice daily was sufficient in this population.

Chapter 8. This chapter describes the occurrence of an outbreak of vancomycin-resistant Enterococcus faecium (VRE) on our haematology ward. A case-control study showed that cases (n = 24) had a longer stay on the ward during the year preceding the outbreak, as compared with VRE-negative control patients (n = 49). More cases had acute myeloid leukaemia and cases had higher grades of mucositis. Logistic regression analysis identified antibiotic use within 1 month before admission and low albumin levels at baseline to be independent risk factors for acquisition of VRE. Control of the outbreak was achieved by a
step-wise implementation of intensive infection control measures, which included the cohorting of patients, allocation of nurses and reinforcement of hand hygiene.

**Conclusions and clinical implications**

The studies described in this thesis have originated from questions and problems that were encountered in daily clinical practice, during the care for patients with haematological malignancies. From the results reported here, some answers to these questions can be deduced, which may contribute to actual and future decisions with regard to the prevention and treatment of infections in these patients:

[1] Levofloxacin may be considered as standard treatment for the prevention of bacterial infections in neutropenic patients, considering its good tolerability and equal efficacy as compared with ciprofloxacin-phenethicillin. Surveillance cultures are mandatory, to closely monitor the emergence of levofloxacin-resistant VG streptococci and adjustments of the prophylactic regimen must be made accordingly.

[2] Amphotericin B colloidal dispersion (ABCD) is not suitable for antifungal prophylaxis in neutropenic patients with a haematological malignancy, due to excessive infusion-related toxicity. If used for therapeutic indications, close pursuit of adverse events is strongly advised.

[3] Exposure to OH-itraconazole may be increased when itraconazole is co-administered with Cyclosporin A. This finding is of limited clinical relevance, but may be important in the occasional event that monitoring of serum itraconazole concentrations is warranted.

[4] The use of cefpirome as empirical antibacterial treatment in patients with febrile neutropenia can not be strongly recommended based on the data presented in this thesis. Though we found a rather good efficacy, there are some points of concern; (a). Limited activity against *Pseudomonas aeruginosa* may in the long run hamper the use of cefpirome as single agent therapy. (b). The use of cefpirome was thought to be associated with the occurrence of an outbreak of vancomycin resistant *Enterococcus faecium*, though chapter 7 nor chapter 8 provide data to fully support this assumption. (c). In a recently published meta analysis on empirical antibiotic monotherapy for febrile neutropenia, cefepime, which closely resembles cefpirome, was associated with a higher mortality rate than other antibiotics, probably due to less efficacy.
[5] Antibiotic use within 1 month before admission and low albumin levels at baseline are independent risk factors for acquisition of vancomycin-resistant *Enterococcus faecium*, during a nosocomial outbreak. Control of the outbreak is achievable, by intensive infection control measures.

**Future directions**

There is now growing evidence that both prophylactic and empirical administration of antibacterial and antifungal antibiotics may reduce mortality and morbidity among patients with severe neutropenia. The data presented in this thesis, however, are too limited to add to the existing evidence on those issues. Our findings rather illustrate the reverse side of the medal, which displays the concerning emergence of resistant pathogens and increased toxicity after the introduction of new prophylactic or therapeutic antibiotics. The large number of reports on anti-microbial resistance and nosocomial outbreaks on haematology or oncology wards, following the application of new prophylactic or therapeutic strategies and to which this thesis adds, can not be neglected.\(^2\)\(^-\)\(^9\) Here, not only the well-being of the individual patient is at risk, but also of the population at large. Moreover, increased toxicity of antibiotics and the emergence of resistant microorganisms may have considerable effects on daily care and management of haemato-oncology units and may substantially increase work load for medical staff and health-care costs.

Although these concerns argue against the widespread and unlimited use of antibiotics in patients with neutropenia, a balanced appraisal is needed, that should give direction to future research.

[1] It is noteworthy that the emergence of resistant strains not necessarily leads to subsequent infection with the microorganism involved.\(^{10}\)\(^-\)\(^12\) The reduction in mortality and infection rates appears to outweigh the detriments of emerging resistant microorganisms. Future studies should not only focus on the development of resistance among potential pathogens, but also on the probability and severity of subsequent invasive infections.

[2] One of the major limitations of the studies described in this thesis is the lack of subdivision of the population of patients as a whole, into different categories of risk levels for infectious complications. For example, patients who are treated with an autologous stem cell
transplantation for Non Hodgkin’s lymphoma are at a different risk and will acquire other types of infections than patients who receive an allogeneic stem cell transplantation for acute leukaemia. To date, efforts are made to distinguish categories of risk of infections among patients with neutropenia.\textsuperscript{13-15} Future studies should aim to identify the population of patients that is likely to benefit from a given agent the most.\textsuperscript{16-18} In selected groups of low-risk patients therapy may be simplified or even discontinued.

\textsuperscript{[3]} Future studies should focus on the development and improvement of sensitive and rapid diagnostic techniques, to trace infectious complications in neutropenic patients. Early detection of bacterial or fungal infections and accurate identification of the pathogens involved, may lead to earlier and more appropriate antibiotic intervention, thereby increasing the success of therapy. In selected groups of patients, improved diagnostic procedures and effective early treatment may even replace prophylaxis and in potential, will reduce the empirical overtreatment of patients with persisting fever during the neutropenic episode.

So, rather than refraining from the routine use of antibiotics in patients with neutropenia, the clinician faces a challenge to chose the right antibiotic regimen for the right population of patients. Not only data from clinical trials should guide these decisions. Other factors, that are at least as important, include local bacteriological and epidemiological data, with an emphasis on resistance patterns of predominantly isolated microorganisms, as well as the utility of an antibiotic in daily practice, its user-friendliness to patients and nursing staff, its toxicity and costs.