The evolution of the empirical management of fever and neutropenia in cancer patients

Claudio Viscoli*

*Corresponding address: University of Genoa, National Institute for Cancer Research, Immunocompromised Host Unit, Largo Rosanna Benzi, 10 16132 Genoa, Italy.
Tel: +39-10-560-0848/6; Fax: +39-10-354-115; E-mail: viscoli@gecuniv.cisi.unige.it

Infectious complications are an important cause of morbidity and mortality in cancer patients, especially those receiving chemotherapy. Furthermore, neutropenia, fever and infection limit the dose-intensity of antineoplastic chemotherapy in cancer patients. Fever without clinical signs of a localized infection is the commonest clinical presentation in neutropenic patients. Early empirical administration of broad-spectrum antibiotics at the onset of fever has become common practice, but the specific empirical regimen remains controversial. Guidance from therapeutic clinical trials is not straightforward, since it is difficult to compare trials, due to major differences and deficiencies in their design and analysis. Clinical trials fall into two categories: (i) explanatory trials which assess the hypothesis under ideal conditions, and (ii) pragmatic trials, which assess the regimen under the conditions of clinical practice. Methodological issues that are of crucial importance in the recognition of limits and value of the results of clinical trials in this field are discussed. The EORTC-IATCG has performed nine large therapeutic trials of empirical antibacterial and antifungal therapy in febrile, neutropenic patients with cancer. The results of trials, V, VIII, IX and XI are reviewed, and issues to be resolved in future trials are also considered.

Introduction

Infectious complications are an important cause of mortality in cancer patients, especially in those receiving chemotherapy. Post-mortem studies have estimated that infection, with or without haemorrhage, is the direct cause of death in about 50–80% of patients dying with acute leukaemia and in about 50% of those dying with malignant lymphoma. In patients with solid tumours, infection is the primary or an associated cause of death in about 50% of cases.1–6 In patients with small-cell lung cancer, ‘toxic’ deaths, i.e. deaths associated with chemotherapy-related toxicity, including infection during neutropenia, may account for up to 20% of the cases in high-risk groups.7 In recent years, infection has emerged as the leading cause of death in other populations of cancer patients, such as those undergoing allogeneic bone marrow transplantation (BMT), probably because of the combined effect of the initial conditioning regimen and of subsequent therapies aimed at controlling graft-versus-host disease. In these patients, and in particular in those receiving bone marrow grafts from unrelated donors, infectious mortality remains high.8,9

The impact of infectious complications on post-chemotherapy morbidity is also relevant. Most episodes of neutropenia lasting more than a week are complicated by fever and in about 50% of these episodes an infection can be documented either on microbiological or on clinical grounds.10 The incidence of fever in patients with solid tumours is considered to be somewhat lower, although figures as high as 70% have been reported in patients with small-cell lung cancer receiving high-dose chemotherapy.11,12 In solid-organ cancer patients the incidence of documented infections has approached 5%, with a 2% infectious mortality. Neutropenia, fever and infection are the most important factors limiting the planned intensity of antineoplastic chemotherapy in cancer patients, sometimes compelling delays in treatment or reduced dosages,
The availability of haematopoietic growth factors has certainly lent a new perspective to treatment. Some clinical trials with these cytokines have shown a significant reduction in the duration of neutropenia, incidence of fever, antibiotic use and length of hospitalization, especially in patients with solid tumors and in those undergoing autologous BMT. However, more severely immunocompromised patients may respond less promptly in terms of granulocyte recovery, and may still experience prolonged periods of neutropenia. In addition, side effects and cost need to be considered.

Fever without clinical signs of a localized infection is the commonest clinical presentation of a potentially overwhelming infection in neutropenic patients and is usually considered a medical emergency. For example, in all therapeutic trials performed by the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), more than half of the patients had no sign of infection other than fever. The incidence and severity of fever and infection in this patient population are inversely related to the absolute neutrophil count and to the duration of neutropenia, and it is highest when the granulocyte count falls below 0.1 \times 10^9/L. If empirical treatment is not promptly undertaken, mortality in severely neutropenic patients with Gram-negative bacteremia can approach 40%. This provides the rationale for the early empirical administration of broad-spectrum antibiotics at the development of fever in this patient population, with substantial improvements in prognosis. However, the specific composition of the empirical regimen remains controversial and subject to change because of the changing pattern of pathogens, the rapid development of bacterial resistance, the emergence of new clinical problems, and the availability of new drugs.

This article reviews (i) the possible choices for empirical therapy for fever and infection in neutropenic patients with cancer; (ii) some methodological issues that are of crucial importance in the recognition of limits and the value of the results of clinical trials in this field; and (iii) the results of the most recent trials performed by the EORTC-IATCG. Finally, the outlook for clinical research on this subject is considered.

**Criteria for selecting an antibiotic regimen**

The majority of physicians involved in the management of febrile, neutropenic cancer patients base the choice of their empirical regimen on local epidemiological data (including pathogen-related and host-related aspects), on general epidemiological studies and on the results of phase III, prospective, randomized, clinical trials comparing new treatments with standard therapy.

**Local epidemiology**

As a general rule, the choice of the empirical antibiotic regimen should be first tailored to local considerations and experience. This is because the type of underlying disease and the antineoplastic regimen used are probably the most relevant factors predisposing to infection, since they influence the duration and severity of the deficit in host defences (mechanical damage, neutropenia). For example, patients with solid tumors have a lower overall incidence of severe infections than patients with acute leukemia or BMT and they can probably be treated with a less aggressive antibiotic regimen when they become febrile during neutropenia. Intensive antineoplastic treatments, such as those used in remission induction of acute leukemias, may increase the risk of severe infectious complications, such as Gram-negative bacteremias, bacterial pneumonia, neutropenic enterocolitis and, especially, fungal infections. A further predisposing factor is the type of intravenous device used. Totally implanted intravenous devices (e.g., Port-a-Cath) are associated with a lower risk of infection than external catheters of the Broviac or Hickman type. The latter are mainly used in leukemic patients. The local bacterial ecology is also important. Clusters of infections caused by specific pathogens have been frequently observed, and may result from several different processes (e.g., construction work, geographical factors, seasonal factors, local patterns of antibiotic resistance due to different antibiotic policies, availability of antibiotics).

**General epidemiology**

In recent years, the prognosis of patients with fever and neutropenia has changed greatly. For example in trial VIII performed by the EORTC-IATCG, the overall mortality rate from any cause, including the underlying disease, 30 days after the onset of fever among more than 800 episodes of febrile neutropenia, including documented infections and fevers of unknown origin, was only 11%. This represents a significant improvement on previous experience such as the third trial (1986), in which the overall mortality was higher than 30%. Survival had improved not only overall, but also in subgroups of patients usually considered to have a more severe prognosis, such as those with documented bacteremia. Among approximately 800 bacteremias observed in EORTC-IATCG therapeutic trials I–V, VIII, IX and XI from 1978 to 1994, the overall mortality rate decreased from 21% to 7% (EORTC-IATCG, unpublished data). In particular, in patients with Gram-negative bacteremia the 30 day mortality rate from all causes (including the underlying disease) is now <10%, while that from Gram-positive bacteremia approaches 6%. This is a dramatic improvement: the mortality rate from Gram-negative rod bacteremia in 1962 approached 90% and in the first
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EORTC-IATCG study in 1978 was >20%\textsuperscript{,27} in the later study, about 15% of patients with Gram-positive sepsis died.\textsuperscript{27} For these reasons, some investigators have recently criticized the indiscriminate use of aggressive intravenous empirical therapies and the need for hospitalization in all febrile, neutropenic patients, suggesting that subgroups of patients at lower risk of unfavourable outcome exist and might be identified and treated accordingly.\textsuperscript{28–31}

The pattern of infective pathogens has also changed significantly over time. For example, several studies have clearly documented that Gram-positive bacteria, which were prevalent in the 1950s and early 1960s, have again become the commonest pathogens.\textsuperscript{32} This trend has been confirmed by the findings of the therapeutic trials that the EORTC-IATCG have performed over the past 22 years.\textsuperscript{24,25,27,33–39} At present, Gram-positive microorganisms are isolated in about 15% of all febrile episodes and cause approximately 60% of all documented bacteraemias.\textsuperscript{39} The reasons for the increasing numbers of Gram-positive infections in these patients remain unclear. Cyclical variation in the type of infecting pathogens has been seen over several decades and may be related to the selective pressure of antibiotics. The treatment of cancer has also become more intensive and is now associated with more severe oral mucositis and diarrhoea, leading to damage to mucosal barriers and increased risk of infection from the resident gastrointestinal flora. Herpes simplex oral lesions are frequently observed in granulocytopenic cancer patients. These infections (or reinfections) can further compromise mucous membrane integrity, allowing bacteria to enter the bloodstream.\textsuperscript{40} In addition, patients with cancer are often fitted with indwelling vascular catheters (especially Broviac or Hickman type, or Port-a-Cath). These devices can easily become colonized by skin bacteria and constitute a well-recognized risk factor for Gram-positive infections. For example, in the fourth EORTC trial,\textsuperscript{34,35} there was an increased proportion of coagulase-negative staphylococcal infections in patients with an indwelling venous catheter when compared with patients without any central catheter (36% vs 15%). The exact role of selective gut decontamination is controversial, since a high incidence of Gram-positive infections has also been documented by investigators who did not use such decontamination.\textsuperscript{41,42}

Systemic prophylaxis with quinolone antibiotics, which is presently used by several oncology centres in Europe, has been advocated as a major cause of the changing pattern of infecting pathogens.\textsuperscript{43} In the fourth EORTC-IATCG trial\textsuperscript{35} only three of 90 patients with Gram-positive bacteraemia received a quinolone prophylactically, suggesting that quinolones are unlikely to be the only contributors to the increased frequency of Gram-positive bacteria. It is probable that the change in the infecting flora is multifactorial in origin.

It is important to realize that the pattern of infecting pathogens might change again and that a high level of vigilance should be maintained. For example, the most recent data from centres of the Italian Association for Paediatric Haematology and Oncology suggest that, in children, Gram-negative bacteria are again increasing in proportion with respect to Gram-positives as the cause of bacteraemias.\textsuperscript{44}

Clinical trials

Choosing the empirical regimen on the basis of results of therapeutic clinical trials is a common approach. However, these trials are difficult to compare, since methodologies, definitions, underlying diseases, pattern of infecting pathogens, microbiological facilities and levels of care are remarkably different. Moreover, many studies have been deficient in statistical design and power. There has also often been confusion between the efficacy of a new antibiotic in febrile, neutropenic patients and its practical utility.

Regimen used

The antibiotic regimens most commonly used for empirical therapy of fever and infection in neutropenic patients are summarized in Table I.\textsuperscript{45} During the past 10 years, regimens for empirical antibiotic therapy in febrile

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<th>Table I. Empirical antibiotic regimens for febrile, granulocytopenic cancer patients\textsuperscript{45}</th>
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neutropenic patients with cancer have included: (i) combinations of a β-lactam antibiotic (a third-generation cephalosporin, carbapenem or ureidopenicillin, with or without β-lactamase inhibitors) and an aminoglycoside (gentamicin, netilmicin or amikacin); (ii) double β-lactam combinations; and (iii) monotherapy, usually with a third-generation cephalosporin, a carbapenem, or a penicillin with a β-lactamase inhibitor. In addition, some investigators have suggested that the inclusion of cover against Gram-positive organisms with a glycopeptide (vancomycin or teicoplanin), either as part of a three-drug regimen (β-lactam, aminoglycoside and glycopeptide) or in combination only with the β-lactam, might be beneficial. More recently, new approaches have been tried, such as once-daily therapy with ceftriaxone and amikacin, and monotherapy with either intravenous or oral quinolones. 

Combination therapy

Several studies have shown that the combination of a penicillin or a cephalosporin with an aminoglycoside is the best therapeutic approach to the treatment of febrile neutropenia. The advantages of such regimens include a potential synergic effect against Gram-negative bacilli, a possible reduction in the emergence of resistant strains both in the individual patient and in the environment and the enlargement of the spectrum of action. Drawbacks of these regimens include poor activity against staphylococci and streptococci, the possible development of resistance in Gram-negative bacilli, and aminoglycoside-related toxicity. The recent introduction of penicillins combined with β-lactamase inhibitors might lend a new perspective to treatment opportunities. The effect of single or multiple daily doses of amikacin given in combination with a β-lactam in neutropenic patients has been extensively studied. Once-daily regimens were not associated with an increase in toxicity and appear to be as effective as multiple daily dose regimens. A nother type of combination which has been mainly used in BMT recipients is a double β-lactam, usually piperacillin and ceftazidime. The two main disadvantages of this type of combination include high costs and the relative unpredictability of the pharmacodynamic behaviour of antibiotics that share the same mechanism of action, while the advantage might be a better coverage of streptococci, owing to inclusion of the ureidopenicillin.

Monotherapy

About 10 years ago, the availability of β-lactam drugs with a broad spectrum of action, such as ceftazidime and imipenem/cilastatin, led several groups to study whether it was possible to treat the febrile, neutropenic patient with a single, broad-spectrum antibiotic. Theoretical advantages of monotherapy over combined therapy include reduced toxicity and improved ease of administration. The results of some clinical trials favoured monotherapy, while others reached the opposite conclusion. The controversy between supporters of monotherapy and supporters of combined therapy continues. The controversy about monotherapy versus combined therapy is largely a result of confusion and misunderstandings between objectives of trials and definitions of success and failure, and genuine mistakes regarding the calculation of the patient sample size necessary for meaningful statistical conclusions. A great deal of discussion has been based on studies with small sample sizes or on results of subgroup analyses that are, by definition, poorly predictive and, therefore, not totally applicable to daily clinical practice. Consequently, there are important limitations in the practical application of the observed results.

In summary, although the issue has never been studied in a suitable number of patients, available evidence suggests that at the end of the neutropenic period there is little difference in terms of survival between febrile, neutropenic patients given empirical monotherapy and those who received combination therapy. However, it is not known what effect either approach might have on the patient's quality of life and on the financial costs to the healthcare system. The general consensus is that selected populations of high-risk patients should receive combination therapy, with early discontinuation of the aminoglycoside in cases of unexplained fever, while other patients could be safely managed with monotherapy. Unfortunately, no study group has been able to discriminate reliably between low-risk and high-risk patients or to distinguish between patients with Gram-negative or Gram-positive bacteraemia at presentation and, therefore, to conduct clinical trials focusing on these patients. Furthermore, no study has addressed the problem from the viewpoints of costs and the patient's quality of life (duration of fever, duration of hospitalization, need for hospitalization, route of administration, number of daily infusions, etc.). In conclusion, there is no convincing evidence that monotherapy is the ‘gold standard’ of empirical antibiotic therapy in febrile, neutropenic cancer patients, although this regimen is probably effective in subgroups of patients with shorter and less severe neutropenia. Resistance to third-generation cephalosporins is increasing, and this may be a cause for concern in centres using monotherapy.

Inclusion of Gram-positive cover in empirical therapy

With regard to the increase in Gram-positive infections, the EORTC trials show that the response rate of these infections decreased significantly from 74% in trial I (1977–1978) to 31% in trial IX (1994–1995), and 28% in trial XI (1995–1996), without increased mortality. The increased incidence and the decreased response rate have led some to propose and to study the inclusion of specific Gram-positive cover in the initial empirical regimen.
Some studies reported favourable results from this practice, with more rapid resolution of fever and reduction in Gram-positive superinfections, total number of febrile days and need to use empirical amphotericin B. In contrast, other groups did not find any significant advantage with empirical Gram-positive cover and suggested that vancomycin should be added to the empirical regimen only upon documentation of a Gram-positive infection not responding to initial empirical treatment. Several factors might explain these discrepancies, including differences in patient characteristics, trial design, antibiotic regimens used, spectrum of pathogens and patterns of antibiotic susceptibility. In most of the above studies, the effect of vancomycin was studied in the setting of a triple antibiotic regimen, in combination with both an aminoglycoside and a β-lactam antibiotic. However, vancomycin might not be as effective when used without aminoglycosides. In a study carried out in children, patients were randomized to receive either ceftazidime plus amikacin or ceftazidime plus vancomycin. The difference in the response rate was not statistically significant (66% in the amikacin group and 77% in the vancomycin group). Similarly, subgroup analysis (bacteraemias, patients with long-lasting and severe neutropenia, etc.) failed to reveal any appreciable difference between the two regimens. This was also confirmed by the results of the multivariate analysis which showed that factors adversely affecting outcome were acute leukaemia (especially non-lymphoblastic leukaemia) and a documented infection (especially a clinically documented infection). In conclusion, in this study, despite the high incidence of Gram-positive infections (64%), the early inclusion of vancomycin did not provide the expected advantage. Six of 12 staphylococcal bacteraemias associated with localized infections, randomized to the vancomycin group, required the addition of another anti-staphylococcal drug; in three of them failure was documented not only on clinical grounds, but also by persistence of positive cultures. Although definitive conclusions cannot be drawn because of the insufficient statistical power of the study, these results suggest that the early inclusion of vancomycin in empirical regimens should not be considered a panacea for all Gram-positive infections. Indeed, such a policy might give a false sense of security against any staphylococcal or streptococcal infection.

It seems logical to conclude that the inclusion of vancomycin in empirical regimens is a correct approach only for individual patients or with signs of infection at the vascular catheter site. In other instances, vancomycin can be safely added upon documentation of infection with methicillin-resistant staphylococci.

Methodological issues

With the aim of standardizing methodologies and definitions used in clinical trials of empirical antibiotic therapy in febrile, granulocytopenic patients, the International Immuno compromised Host Society, the Infectious Disease Society of America, and the European Society of Clinical Microbiology and Infectious Disease have published consensus reports. These documents should be read and followed by all those involved in the design and implementation of clinical trials in these patients. Although representing progress in the area, these publications dealt with general principles without focusing on specific methodological aspects. We have recently addressed the problem, utilizing clinical, epidemiological and statistical expertise, with the aim of guiding the clinician through critical evaluation of the results of clinical trials, i.e. their qualities, problems and limitations.

Within the design of phase III clinical trials, two approaches co-exist: the ‘explanatory’ approach and the ‘pragmatic’ approach. The usual aim of an explanatory trial is to test a therapeutic hypothesis under ideal conditions, while the aim of a pragmatic trial is to assess the effectiveness of a treatment in actual clinical practice. The specific aims of most clinical trials of empirical antibiotic therapy in febrile, neutropenic cancer patients are not free from ambiguity. The usual explicit aim has been that of comparing the ‘efficacy’ of two regimens. However, ‘efficacy’ has been more frequently judged by the antibacterial activity of the regimen under study (explanatory aim) rather than by the practical benefits it brings to the overall patient population treated (pragmatic aim). These two endpoints are often taken as interchangeable but, in fact, they are completely distinct (although not independent) treatment effects. A antibacterial activity is a necessary but not exclusive condition for a beneficial effect for the patients. This is not a trivial distinction, since the difference in aims results in profound methodological differences. Much of the controversy over the interpretation of the results of clinical trials of empirical antibiotic therapy in febrile, granulocytopenic cancer patients arises simply from a failure to appreciate the relationships between the objectives and the design of the trial, and ‘from disagreements (often unrecognized) or ambiguities over the questions posed by these trials’.

Study design in explanatory trials

The specific objective of explanatory trials is the assessment of antibacterial activity. For this reason the conclusions cannot be directly transferred to clinical practice, unless exceptionally favourable results are observed. The appropriate endpoint in these trials is success or failure in those patients with the specific documented infection for which the study drug is being given. For a number of reasons that are peculiar to febrile, neutropenic patients, many who are randomized will be excluded from the efficacy analysis because they had other types of infection or an unexplained fever. In these studies, randomization should preferably be double-blind. Success should be
defined as defervescence, clearance of signs of infection and clearance of bacteraemia. These are strong endpoints if the trial focuses on documented infections, while they become much weaker when applied to unexplained fevers. Every modification of the initial antibacterial regimen should be considered as a failure. A randomization analysis of the proportion of patients remaining febrile on each day of treatment in the two arms of the study would be helpful, with the aim of detecting differences in terms of management of the same clinical situation (e.g. persistence of fever). In addition, a statement should be included in the trial protocol, regarding the policy to be adopted when a pathogen resistant to the allocated antibiotic(s) is isolated as the cause of infection in a patient who is nevertheless clinically responding. A patient should be evaluated for response to treatment (according to the 'intention-to-treat' principle), independently of compliance with the assigned treatment, but an analysis should also focus on the subgroup(s) for which the study was designed. The sample size for an explanatory study should be calculated based on the observed (historical) response to treatment in the specific subset of patients under study and on the improvement in the rate that can be expected. The number of patients to be randomized should then be calculated based on the expected proportion of specific target patients within the overall population of febrile, neutropenic patients.

Most trials of empirical antibiotic therapy in febrile, neutropenic patients conducted in recent years, including some of the trials performed by the EORTC-IATCG, belong in this category. However, because of the above-mentioned ambiguity, their results have been widely applied to clinical practice. Most of the trials have shown that combination therapy is better than monotherapy in subgroups of febrile, neutropenic cancer patients, but they have failed to show the same result in the overall population of randomized patients.

Study design in pragmatic trials

Once the activity and the toxicity of a new treatment have been evaluated, the requirement is to know whether it is more convenient (or equally convenient) to use the new treatment, instead of the standard one, in the ‘typical’ febrile, neutropenic patient. By ‘typical’ is meant any patient presenting with fever and neutropenia (regardless of the final diagnosis) in routine clinical activity, and in the absence of any specific characteristic (e.g. age, concomitant disease, short-term prognosis, clinical presentation specific to or highly suggestive of a particular aetiology) that requires an individualized approach. For this purpose a ‘pragmatic trial’ is required in order to produce results that can be directly transferred to clinical practice. Few, if any, true pragmatic trials of empirical antibiotic therapy in cancer patients have been reported.

Pragmatic trials of empirical antibiotic therapy in febrile neutropenic cancer patients present several methodological problems. First, all randomized patients should be included in the analysis, independent of the final diagnosis and of treatment compliance. This ‘intention-to-treat’ principle is warranted by the need to avoid bias from the exclusion of non-compliant patients, and by the need to preserve the generality of the results. A second problem is the identification of the appropriate outcome measure (endpoint). A randomization analysis of efficacy based on the proportion of clinical ‘success’ has several shortcomings when used in pragmatic trials, where a treatment is successful inasmuch as it positively affects quality of life and/or mortality. Whether (and how consistently) an increase in the proportion of ‘clinical’ success is correlated with decreased mortality or with an improvement in quality of life remains to be demonstrated. Moreover, it is difficult to use this definition in episodes of fever not positively linked to an infectious aetiology (e.g. unexplained fevers). Also, some investigators consider persistence of fever as a marker of failure, requiring treatment change, while others consider the patient as clinically stable, although still febrile, and continue the same treatment.

Based on these considerations, some investigators, especially those advocating monotherapy, have used survival as the main endpoint in trials aimed at assessing treatment efficacy. Indeed, if one considers that the rationale for administering empirical antibiotic therapy is to decrease early mortality from bacterial infections, one should agree that the best definition of success is a patient’s survival at the end of the neutropenic period. Unfortunately, the use of survival as the outcome variable in episodes of febrile neutropenia is difficult, especially because the overall mortality rate from any cause at 30 days from the onset of fever is now relatively low, thus making any further improvement difficult to detect and probably of little clinical significance. In any case, a study having mortality as the primary endpoint would require a large sample size, a difficult problem even for large, multicentre groups. For instance, a trial aimed at detecting a 3% absolute reduction in mortality (from 8% to 5%) with a power of 80%, would require more than 2000 patients. Those trials that used survival as the main endpoint of efficacy, however, calculated sample size not from the historical and expected survival rate but rather on the ‘clinical’ response rate.

A randomization analysis of a trial having survival as the endpoint should also be strictly by intention-to-treat, without differentiating between those cases in which success was obtained through multiple treatment modifications and those that did not require any treatment change.

Investigators should resist the temptation of drawing conclusions concerning the antibacterial activity of the study drugs. This does not mean that the issue of treatment modification is a negligible one. The frequency of treatment modifications in either arm should be taken into...
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Account in the interpretation of the results, especially as far as quality of life and costs are concerned. A non-prohibitive number of patients is required for trials using survival as the main endpoint. A desirable alternative would be to identify subgroups of patients at high risk of death, and to concentrate clinical and research efforts on these patients. Meanwhile, it is reasonable to expect that a ‘clinical’ definition of success will continue to be the main endpoint in most of the trials in this area. Since many of these trials will have pragmatic aims, interpretation of the results must bear the above limitations in mind.

The EORTC-IATCG trials

In 1973, the IATCG of the EORTC was founded to study infections in cancer patients and to investigate a better approach to the febrile, neutropenic patient. The EORTC is an international, multicentre association that is dedicated to the improvement of knowledge in the field of cancer. The EORTC-IATCG has its data centre at the Institut Jules Bordet in Brussels, and includes centres from several European and non-European countries. The internal organization includes an Advisory Board, a Management Board and a Data Review Committee. The Advisory Board is mainly concerned with conceiving and designing new studies and with legal and financial matters, while the Management Board is more deeply involved in the practical management of the Group. The Data Review Committee meets approximately every other month at the data centre to review all clinical report forms sent from the various centres participating in trials, after the Data Manager has made a preliminary review. The Group monitors its own trials by performing site visits and audits according to Good Clinical Practice rules.

At the time of writing, the IATCG has published the results of nine large therapeutic trials of empirical antibacterial and antifungal therapy in febrile, neutropenic patients with cancer and two trials of prophylaxis, undertaken from 1978 to 1995. The results of four clinical trials of empirical antibiotic therapy, performed between 1978 to 1985, have been reviewed elsewhere. I will briefly review the results of trials V, VIII, IX and XI, i.e. four other therapeutic trials completed. A nother therapeutic trial (trial VI) has been completed and published, but there were major differences between patient populations with respect to the other trials. Trial VI compared monotherapy with ciprofloxacin, 200-300 mg every 12 h, with combined therapy with piperacillin and amikacin in a selected population of febrile, neutropenic patients with lymphoma and solid tumours. The trial was discontinued prematurely because patients treated with ciprofloxacin had a statistically significantly poorer response rate at an interim analysis (65% vs 95%, P = 0.002) with a 14.5% death rate in evaluable patients compared with 6% in the other treatment arm. This difference was probably due to an inadequate dosage of ciprofloxacin.

Trial V

Trial V was conceived and designed in 1986 in response to the increasing role of Gram-positive cocci (streptococci and staphylococci) in infection in cancer patients and their reduced response rate to several empirical regimens. Of note, the decreasing clinical response rate was not accompanied by increased mortality (4% in trial IV). The trial was completed in early 1988 and the results published in early 1991. The hypothesis tested was that the addition of vancomycin to ceftazidime plus amikacin at the onset of fever would have been beneficial. Briefly, 747 episodes of fever and neutropenia in patients with cancer were randomized to receive ceftazidime plus amikacin with or without vancomycin. Initial analysis of the results showed that the overall response rate in the group of patients receiving vancomycin was much better than that seen in the control group (76% vs 63%; P < 0.001). This was particularly evident in the population of patients with Gram-positive bacteraemia, in which the addition of vancomycin resulted in a response rate of 72% compared with 43% in the control group (P < 0.001). However, when the reasons for failure were analysed in detail, most failures were found to be a lack of clinical response with persistence of fever, and that such failure (i.e. treatment change) occurred very soon after the onset of fever. In none of the Gram-positive bacteraemias was failure due to objective reasons such as persistence of pathogen or development of septic shock: only three infection-related deaths were reported (none in the first 3 days of empirical therapy). As shown in Figure 1, a comparison of the febrile days in the two treatment groups indicated that, faced with the same clinical situation (i.e. persistence of fever), a different approach was used in the patient groups: in patients randomized to ceftazidime and amikacin investigators added vancomycin (a criterion defining failure), while in those already receiving vancomycin, they did not change treatment. Therefore, the better response rate was not genuine and was due not to true failures but simply to physician prejudices. Conversely, antifungal agents were added to the protocol therapy in only three patients receiving ceftazidime and amikacin but in 11 receiving the same regimen plus vancomycin.

In this trial we obtained important information about how haematologists and oncologists manage febrile neutropenia. As a general rule, the more prolonged the neutropenia and fever, the more likely it is that physicians add or replace antibiotics even in the absence of objective reasons for doing so. Changing therapy would obviously be an appropriate practice if cultures remain persistently positive, if the patient remains febrile (peaking at more than 39°C) and deteriorates, or if the infection is due to a resistant strain. It is much less appropriate (especially in
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patients with unexplained fever) when there is no objective sign of clinical deterioration, when cultures are negative (or have become negative), and when the only reason for changing therapy is persistence of fever. In particular, the practice of adding a glycopeptide antibiotic is not based on the results of controlled studies and it is frequently based on subjective factors. In general, the lower the number of antibiotics that are part of the initial regimen, the higher the number of modifications, most of which are not justified either on clinical or microbiological grounds. The trial did show that granulocytopenic patients with Gram-positive infections not responding to initial therapy can be successfully treated with vancomycin added after identification of the infecting organism, and that the use of vancomycin from the onset of fever did not result in a more rapid defervescence. Bearing in mind the recent increase in glycopeptide resistance, glycopeptide antibiotics should not be used indiscriminately in febrile neutropenic patients. Several studies in vitro and in animal models and some pilot studies in humans had shown that aminoglycosides could be given effectively as a single, large, daily dose of amikacin, in combination with a long-acting cephalosporin (ceftriaxone), also given once daily, was compared with a combination of amikacin and ceftazidime, each given in three separate daily doses. The rationale behind the study was that aminoglycosides have rapid bactericidal activity and show concentration-dependent killing and post-antibiotic effects, all features favouring regimens able to achieve high peak serum concentrations. The results of the trial are summarized in Table II. Briefly, the response rate among 350 episodes treated with a single-daily dose of ceftriaxone plus amikacin was 71%, compared with 74% in 344 patients treated with the traditional amikacin-ceftazidime regimen. Efficacy was similar in all patient subgroups, including those with Gram-positive or Gram-negative bacteraemia. Of note, in this trial there were only 47 Gram-negative bacteraemias (6.7% of all evaluable episodes), 20 due to E. coli, ten to Pseudomonas spp., four to Klebsiella spp. and 13 to other Gram-negative bacilli. Efficacy in the patients with Gram-positive

### Table II. Efficacy results in EORTC-IATCG trial VIII (reproduced, with permission, from EORTC-IATCG)

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<thead>
<tr>
<th>Type of infection</th>
<th>Single daily amikacin plus ceftriaxone</th>
<th>Multiple daily amikacin plus ceftazidime</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>249/350 (71)</td>
<td>256/344 (74)</td>
<td>-3 (-10 to 3)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Microbiologically documented</td>
<td>54/101 (53)</td>
<td>59/104 (57)</td>
<td>-4 (-17 to 10)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>40/80 (50)</td>
<td>46/90 (51)</td>
<td>-1 (-16 to 14)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>single Gram-positive</td>
<td>24/54 (44)</td>
<td>22/50 (44)</td>
<td></td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>coagulase-negative staphylococci</td>
<td>9/24 (38)</td>
<td>6/15 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2/4</td>
<td>4/9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>viridans streptococci</td>
<td>11/23 (48)</td>
<td>10/20 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other streptococci</td>
<td>2/3</td>
<td>1/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other Gram-positive bacteria</td>
<td>0/0</td>
<td>1/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single Gram-negative</td>
<td>13/20 (65)</td>
<td>19/27 (70)</td>
<td></td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3/5 (60)</td>
<td>11/15 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1/5</td>
<td>3/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>1/2</td>
<td>2/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other Gram-negative bacteria</td>
<td>8/8</td>
<td>3/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>polymicrobial</td>
<td>3/6 (50)</td>
<td>5/13 (39)</td>
<td></td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Non-bacteraemic</td>
<td>14/21 (67)</td>
<td>13/14 (93)</td>
<td></td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Clinically documented</td>
<td>84/108 (78)</td>
<td>63/83 (76)</td>
<td>-2 (-10 to 14)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>111/141 (79)</td>
<td>134/157 (85)</td>
<td>-6 (-15 to 2)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**Trial VIII**

Trial VIII was conceived and designed in 1989 with the objective of showing that any patient presenting with fever and neutropenia in routine clinical practice, regardless of the final diagnosis and other specific characteristics, could be treated successfully with an antibiotic regimen given once daily, with obvious advantages in terms of cost reduction and patient convenience. Although not explicitly stated, this trial was considered as preliminary to a trial of once-daily out-patient therapy. A single, large, daily dose of amikacin, in combination with a long-acting cephalosporin (ceftriaxone), also given once daily, was compared with a combination of amikacin and ceftazidime, each given in three separate daily doses. The rationale behind the study was that aminoglycosides have rapid bactericidal activity and show concentration-dependent killing and post-antibiotic effects, all features favouring regimens able to achieve high peak serum concentrations. Several studies in vitro and in animal models and some pilot studies in humans had shown that aminoglycosides could be given effectively as a single, large, daily dose without increased toxicity. The results of the trial are summarized in Table II. Briefly, the response rate among 350 episodes treated with a single-daily dose of ceftriaxone plus amikacin was 71%, compared with 74% in 344 patients treated with the traditional amikacin-ceftazidime regimen. Efficacy was similar in all patient subgroups, including those with Gram-positive or Gram-negative bacteraemia. Of note, in this trial there were only 47 Gram-negative bacteraemias (6.7% of all evaluable episodes), 20 due to E. coli, ten to Pseudomonas spp., four to Klebsiella spp. and 13 to other Gram-negative bacilli. Efficacy in the patients with Gram-positive
Empirical antibiotic therapy of febrile neutropenia

bacteraemias was unsatisfactory in both arms. Although the patient sample size in this trial was not calculated on the expected proportion of patients with Gram-positive bacteraemia and, therefore, the statistical power of the observed differences was low, and although true failures were rare, it is of concern that the response rate in these episodes was only 44% in either arm. As shown in Table III, the toxicity results were surprising. Not only did a single, large, daily dose of amikacin, achieving peak levels as high as 75 mg/L (median 45.5 mg/L), not result in more nephrotoxicity than the divided-dose regimen (3% in the single-daily dose group, and 2% in the control group), but the increase in serum creatinine was smaller, occurred later in the single-daily dose group and was primarily seen when other nephrotoxic agents were added. Similarly, ototoxicity, which was measured in 144 patients (21% of the study sample), was not higher in the single daily dose group. The conclusion of this study was that amikacin in combination with a third-generation cephalosporin, could be safely given once daily to febrile, neutropenic patients.

Trial IX

In trial IX, the EORTC-IATCG introduced two important methodological modifications regarding the definition of failure. First, in previous trials there had been no control on the policy to be implemented when a pathogen resistant to the allocated antibiotic(s) was isolated in a patient who was nevertheless responding ‘clinically’ to treatment. Some investigators had changed treatment regardless of any clinical consideration, while others adopted a more pragmatic approach, not changing therapy if the patient was clinically responding to treatment and the pathogen was eradicated. This discrepancy might have caused biases in the evaluation of the treatment results. For this reason it was decided that infections caused by pathogens resistant to the allocated β-lactam drug would be classified as failures, regardless of the patient’s clinical response. This led to a stronger failure endpoint and to a reduction in the response rates. Second, the analysis was performed only on episodes considered evaluable by the Data Review Committee, which meant the exclusion of non-bacterial infections, protocol violations, etc. This approach, shared by many similar studies, was no longer considered acceptable. The analysis of results in trial IX was performed both on evaluable patients and on all randomized patients, based on an intention-to-treat approach.

The objective of trial IX was to investigate whether an extended-spectrum penicillin combined with a β-lactamase inhibitor would improve the coverage of Gram-positive infections while retaining good activity against Gram-negative bacteria. An in-vitro study of 365 pathogens isolated from previous trials had shown that a combination of piperacillin and tazobactam had a comparable activity to that of ceftazidime against Gram-negative bacteria (with the exception of Pseudomonas spp.), while it was more active against Gram-positive cocci. There were few concerns about a possible lower efficacy of piperacillin/tazobactam in infections caused by Pseudomonas spp., since, in trial VIII, Pseudomonas spp. had been isolated in only 1% of all febrile episodes and in 7% of all single-agent bacteraemias (compared with 3% and 11% in trial I). The efficacy and toxicity of piperacillin/tazobactam and ceftazidime, each in combination with single-daily amikacin, were compared. The results are summarized in Table IV. Briefly piperacillin/tazobactam plus amikacin performed better than ceftazidime plus amikacin. Overall, the former regimen was successful in 61% of 342 episodes compared with 54% of 364 treated with the latter (P = 0.05). As shown in Figures 2 and 3, in patients receiving piperacillin/tazobactam, the time to deferves-
cence was significantly shorter than that observed in the control group \((P = 0.01)\), and the time to failure significantly longer \((P = 0.02)\). Although the primary objective of the trial was not to test the study drugs in patients with bacteraemia (and therefore the patient sample size was not calculated on the expected proportion of patients with bacteraemia), nevertheless the results in the subgroup of bacteraemic infections were reported. In this subgroup, a significant difference in response rate was found, with piperacillin/tazobactam resulting in a 50% success rate and ceftazidime in 35% success \((P = 0.05)\). Piperacillin/tazobactam plus amikacin performed better than ceftazidime plus amikacin in single Gram-positive, single Gram-negative and polymicrobial bacteraemias but the differences were not statistically significant. The performance of piperacillin/tazobactam in Gram-positive bacteraemias was probably impaired by the high proportion of methicillin-resistant coagulase-negative staphylococci that caused 36% of the single Gram-positive bacteraemias and were assessed by definition as failures.

**Trial XI**

In this trial two methodological innovations regarding the randomization procedure were introduced. In previous trials a patient could have been randomized more than once, for different episodes of fever, provided these were not occurring during the same period of neutropenia. This approach had been criticized by some peer reviewers, because potentially able to bias results. Therefore, in this trial only one randomization per patient was allowed. Moreover, in previous trials randomization was not centralized. Investigators were provided with sealed envelopes and randomization was performed by opening consecutive numbered envelopes, which were then forwarded to the Data Centre. In trial XI, patients were randomized centrally by telephoning the IATCG randomization computer at the IATCG Data Centre in Brussels. The computerized randomization system was accessible 24 h a day, 7 days a week.

Trial XI was designed to give a definitive answer to the question of the efficacy of monotherapy versus combined therapy. Meropenem, a carbapenem which is not metabolized at any level in the body and is excreted unchanged in urine, was compared with ceftazidime plus amikacin. The results of the study were published in 1996. \(^{39}\) Of 1034 randomized patients, 958 were assessable in the intention-to-treat analysis for response to therapy, 483 in the meropenem arm and 475 in the ceftazidime/amikacin arm. Treatment was judged successful in 270 (56%) receiving meropenem and in 245 (52%) receiving combination therapy. The success rates were similar by type of infection and by underlying disease. The incidence of further infection was also similar between the two groups. Mortality was very low (1.6% in the meropenem group and 2.7% in the ceftazidime/amikacin group). Treatment was judged successful in 270 (56%) receiving meropenem and in 245 (52%) receiving combination therapy. The success rates were similar by type of infection and by underlying disease. The incidence of further infection was also similar between the two groups. Mortality was very low (1.6% in the meropenem group and 2.7% in the ceftazidime/amikacin group). This study showed unequivocally that monotherapy with meropenem is safe and feasible. However, other issues should also be taken into account, such as cost and ability to induce β-lactamase production. In addition, since meropenem is one of the widest spectrum antibiotics available and is active against many Gram-negative bacteria that are resistant to other drugs, it probably should not be used as first line therapy.

### Table III. Toxicity results from EORTC-IATCG trial VIII (reproduced, with permission, from EORTC-(IATCG 24))

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Single daily amikacin plus ceftriaxone</th>
<th>Multiple daily amikacin plus ceftazidime</th>
<th>Difference (95% CI) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>351</td>
<td>345</td>
<td></td>
<td></td>
</tr>
<tr>
<td>without other nephrotoxic agents</td>
<td>12 (3%)</td>
<td>11 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with other nephrotoxic agents</td>
<td>1 (3%)</td>
<td>11 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range) increase in serum creatinine (μmol/L)</td>
<td>75 (50–300)</td>
<td>120 (60–215)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range) to onset of nephrotoxicity (days)</td>
<td>10 (7–14)</td>
<td>10 (7–14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory toxicity</td>
<td>6/70 (9%)</td>
<td>5/74 (7%)</td>
<td>2 (–2 to 11)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>without other ototoxic agents</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with other ototoxic agents</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bilateral</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range) decrease (dB)</td>
<td>27.5 (20–50)</td>
<td>27.5 (20–50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular toxicity</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)Number of patients with abnormal audiograms/total number of patients with audiograms evaluable.
Empirical antibiotic therapy of febrile neutropenia

Table IV. Efficacy in EORTC-IATCG trial IX (reproduced, with permission, from Cometta et al.38)

<table>
<thead>
<tr>
<th>Infection or pathogen</th>
<th>Piperacillin-tazobactam + amikacin</th>
<th>Ceftazidime + amikacin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall rate</td>
<td>210/342 (61)</td>
<td>196/364 (54)</td>
<td>0.05</td>
</tr>
<tr>
<td>Microbiologically documented infections</td>
<td>49/93 (53)</td>
<td>43/112 (38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>40/80 (50)</td>
<td>35/101 (35)</td>
<td>0.05</td>
</tr>
<tr>
<td>Single Gram-positive bacteraemia</td>
<td>20/52 (38)</td>
<td>14/56 (25)</td>
<td>0.19</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>3/24 913</td>
<td>3/28 (10)</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>3/6</td>
<td>1/4</td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>13/20 (65)</td>
<td>10/20 (50)</td>
<td></td>
</tr>
<tr>
<td>Other Gram-positive bacteria</td>
<td>1/2</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>Single Gram-negative bacteraemia</td>
<td>18/24 (75)</td>
<td>18/29 (62)</td>
<td>0.38</td>
</tr>
<tr>
<td>E. coli</td>
<td>9/10 (90)</td>
<td>8/12 (67)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella and/or Enterobacter spp.</td>
<td>3/6</td>
<td>4/5</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3/4</td>
<td>2/6</td>
<td></td>
</tr>
<tr>
<td>Other Gram-negative bacteria</td>
<td>3/4</td>
<td>4/6</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial infections</td>
<td>2/4</td>
<td>3/16 (19)</td>
<td></td>
</tr>
<tr>
<td>Nonbacteraemic infections</td>
<td>9/13 (69)</td>
<td>8/11 (73)</td>
<td></td>
</tr>
<tr>
<td>Clinically documented infections</td>
<td>65/105 (62)</td>
<td>54/105 (51)</td>
<td>0.16</td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>96/144 (67)</td>
<td>99/147 (67)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Figure 2. Time to defervescence in EORTC-IATCG trial IX. Patients treated with piperacillin/tazobactam plus amikacin (—) had a shorter duration of fever than those treated with ceftazidime plus amikacin (—). (Reproduced, with permission, from Cometta et al.38)

Figure 3. Time to failure in EORTC-IATCG trial IX. Patients treated with ceftazidime plus amikacin (—) failed earlier than those treated with piperacillin/tazobactam (—). (Reproduced, with permission, from Cometta et al.38)

New approaches to empirical therapy of febrile neutropenia

In recent years it has become more widely acknowledged that patients with cancer, granulocytopenia and fever are not all the same, and that both the cause of fever and the clinical course may vary considerably. According to this concept, the empirical therapy for febrile neutropenia in cancer patients should not be the same in every situation and in every patient, but might, and probably should, be modulated according to individual risk factors. Accordingly, some studies have shown that early discharge with
out-patient treatment and short-term antibacterial therapy is feasible and safe in selected groups of patients and that it is not always necessary to continue intravenous antibiotic therapy until recovery from neutropenia. Some authors have gone further. For example, in a pragmatic, randomized study, investigators at the MD Anderson Cancer Center in Houston, Texas showed that out-patient treatment was as safe as the traditional in-hospital approach in a selected group of febrile, neutropenic cancer patients, free from any type of co-morbidity (alterations of renal and hepatic parameters), and staying in a range of 50 km (30 miles) from the cancer centre. In Italy, single-daily ceftriaxone plus amikacin was successfully tested as an out-patient treatment, and investigators from Pakistan published two studies of oral therapy for febrile neutropenia. In the first study 122 febrile neutropenic patients, half of whom had a haematological malignancy, were randomized to receive oral therapy with ofloxacin, a broad-spectrum fluoroquinolone, or an intravenous combination of a penicillin (carbenicillin, cloxacinil, piperacillin) and amikacin. In the second study, 111 patients with lymphomas or solid tumours were discharged home with a prescription to take oral ofloxacin in the case of fever. A bout 80% of the patients who developed fever were cured with this therapy, without readmission to hospital. Although these results should be treated with great caution because of the small sample size and other important methodological problems (variable composition of the control-drug regimen in the first study, confused definition of success and failure, lack of information about the number of eligible patients not enrolled because they were unable to take oral medications, poor clinical control and poor study control), they suggest that, at least in that area of the world and in 'low-risk' patients, oral and intravenous therapy might perform similarly and self-medication is feasible.

In all these studies the choice of patient for out-patient care or oral therapy was not based on any risk assessment or predetermined rules, but rather on clinical judgement. Clinical judgement is obviously important but the problem remains how scientifically to identify, at the development of fever, the subgroup of patients likely to have a favourable outcome in order not to put some patients at unacceptable risk and not to use unnecessary, aggressive, antibiotic therapies.

With this in mind, Talcott and co-workers analysed data available within the first 24 h after the onset of fever in granulocytopenic patients in order to identify those at lower risk of an unfavourable course and, therefore, most likely to benefit from early discharge and out-patient care. In this analysis the dependent variable was defined as the development of severe medical complications, including infection. A long list of such complications was provided. Judgements were based on a prospective evaluation partially combined with a blind retrospective review performed by an independent physician. Patients' risks of developing complications were classified according to control of cancer, presence of co-morbidity factors and type of care (out-patient or in-patient), and four risk groups were identified. Out-patients with a controlled cancer and without any co-morbidity factor were more likely to recover easily and rapidly from their episode of fever and granulocytopenia. The results were validated on an independent set of data. A s expected, complications occurred less frequently among out-patients with controlled cancer and without any co-morbidity than in other patients, and a multivariate analysis of factors associated with a favourable outcome showed that the pre-defined risk groups were independently and significantly correlated with the development of complications. Unfortunately, in this study the individual patient risk of complications, calculated on the basis of the mathematical model, was not evaluated, and the sensitivity and specificity of the model (i.e. its discriminatory capacity) were not calculated. In a third study by the same group of investigators the clinical rule appeared not to be able to discriminate satisfactorily between favourable and unfavourable outcomes, since 14 out of 30 patients (47%) discharged 2 days after the onset of fever had to change treatment and nine (30%) had to be readmitted to hospital because of the development of medical complications.

A nother attempt at describing a model for the high-risk patient was performed by our group, focusing on a simpler, more objective, dependent variable, i.e. a diagnosis of bacteraemia. Bacteraemia is known to be associated with some incremental risk of complication and clinical deterioration and the therapeutic results obtained in clinical trials of empirical therapy are usually poorer in bacteraemic patients than in other patients. A total of 834 episodes of fever developing in 771 neutropenic patients were divided into two groups, using a computer-generated randomized procedure. The first group of 558 episodes was used to derive the multivariate model (derivation set), while the second group (276 episodes) was used to assess the discriminating ability of the model (validation set). Characteristics evaluated were gender, age, presence (and type) of an intravenous line at the onset of fever, underlying disease, number of patients randomized by each institution (reflecting the 'size' of the institution), administration of antifungal and antibacterial prophylaxis, duration of granulocytopenia before fever, initial granulocyte and platelet counts, highest temperature before inclusion in the study during the previous 12 h, presence of shock and, finally, an identifiable site of infection at presentation. The results of the multivariate analysis in the derivation set were used to develop a clinical prediction model and the accuracy of this model in discriminating patients with and without a diagnosis of bacteraemia (sensitivity and specificity at various risk cut-off points) was evaluated both in the derivation and in the validation sets using a receiver-operating characteristic (ROC) curve. The results showed that shock, very high fever, an identifiable focus of infection, long-lasting granulocyto-
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Penia, thrombocytopenia and administration of antifungal prophylaxis were predictive of bacteraemia in our patient population. Weaker predictive factors included the size of the institution where the patient was treated, the underlying disease and the administration of antibacterial prophylaxis. A ge, gender, intravenous line and granulocyte count at onset were not associated with diagnosis of bacteraemia. Unfortunately, the clinical prediction rule derived from our data poorly discriminated episodes with bacteraemia from other episodes. A t best, it allowed a reliable prediction for a small subgroup of patients at lower risk.

In conclusion, several issues remain open for consideration to improve anti-infective care in the febrile and neutropenic patient. Some possible hypotheses that deserve more study are listed in Table V. Even though mortality is relatively low and probably strongly related to the degree of control of the underlying disease, morbidity is still high. At present, the development of validated risk profiles represents the best approach to the study of infectious complications in cancer patients, with the twin aims of improving our understanding of this clinical condition and of rationalizing patient care.

Acknowledgement

I would like to thank Mrs Laura Veroni for her assistance in the preparation of the manuscript.

References


Table V. Suggested hypotheses to be tested in future trials of empirical therapy in febrile neutropenia (adapted from Viscoli et al.62)

| New drugs in standard combination regimens | Is a new broad-spectrum antibiotic (a cephalosporin, a carbapenem, a ureidopenicillin, with or without a β-lactamase inhibitor or a quinolone) more effective, as effective as but less toxic, or as effective as but less expensive than standard β-lactam regimens, in combination with the same aminoglycoside? |
| New drugs in monotherapy | Is monotherapy (a cephalosporin, a carbapenem, a ureidopenicillin, with or without a β-lactamase inhibitor, or a quinolone) in combination with placebo as effective as and less toxic and expensive than the standard β-lactam-aminoglycoside combination? |
| Once-daily dose | Is once-daily monotherapy safe and effective? |
| Early antifungal coverage and new antifungal drugs | Is there an advantage in starting empirical antifungal therapy at the development of fever rather than in persisting fevers? |
| Pre-emptive therapy | Is there a difference in terms of efficacy, toxicity or cost between starting an empirical antibiotic regimen at neutropenia (neutropenia-oriented empirical therapy) or at fever (fever-oriented empirical therapy) in cancer patients at high risk of bacteraemia or other medical complications? |
| Early discharge or out-patient treatment | Is there a difference in terms of efficacy, toxicity or cost between in-patient or in-patient treatment of febrile neutropenia in patients at low risk of bacteraemia or other medical complications? |
| Clinical prediction rules | Is it possible to individualize empirical treatments according to patient’s generic risk of severe infection or to patient’s probability of a specific aetiology? |
| Oral treatment | Is there a difference in terms of efficacy, toxicity or cost between standard intravenous treatment and oral treatment? |
| Intravenous-oral sequential treatment | Is there a difference in terms of efficacy, toxicity or cost between standard intravenous treatment with a given drug and the sequential use of two dosing forms or of two routes of administration of the same drug? |


33. EORTC International Antimicrobial Therapy Cooperative
Empirical antibiotic therapy of febrile neutropenia


