Pergamon

European Journal of Cancer Vol. 33, Suppl. 4, pp. S44–S49, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00148-2

Antimicrobial Therapy in Cancer Patients: Studies from the EORTC International Antimicrobial Therapy Cooperative Group

S.H. Zinner

Department of Medicine, Brown University, Division of Infectious Diseases, Rhode Island Hospital and Roger Williams Medical Center, 825 Chalkstone Avenue, Providence, Rhode Island 02908, U.S.A.

Patients with cancer are subject to infections as a result of several factors, notably obstruction or constriction of airways or ducts, erosion of tumour involving the protective integument or mucosa, alteration of host defenses secondary to infiltration of bone marrow, reduced or altered immunoglobulin or cytokine production, or as a result of chemotherapy. Specific infecting organisms may be predicted based on the specific defect in host defenses. For example, patients with myeloma or lymphocytic leukaemia may develop infections with encapsulated bacteria as a result of decreased B-lymphocyte numbers or function, and those with lymphomas may incur a variety of intracellular bacterial, fungal, and viral infections as a result of decreased T-lymphocyte function. Neutropenia is the most frequently encountered host cell defect in patients with cancer and predicts the development of bacteraemia caused by Gram-positive and Gram-negative bacteria. Recent changes in microbial ecology and antimicrobial resistance profiles have highlighted the need for continued reevaluation of antimicrobial therapy in these patients. Several new antibiotics with enhanced activity against organisms frequently isolated from patients with cancer have been introduced and studied recently. The International Antimicrobial Therapy Cooperative Group of the EORTC has studied meropenem alone, piperacillin/tazobactam, and ceftriaxone, each with single daily dose amikacin; these regimens compare favourably with ceftazidime plus amikacin for empirical treatment of fever in neutropenic patients. Preventive measures are important, if understudied, and the optimal antibiotic approach to prophylaxis remains unclear. Adjunctive measures including prophylactic and therapeutic colony-stimulating factors play an important role. © **1997 Published by Elsevier Science Ltd.**

Key words: antibiotics, antimicrobial therapy, bacterial infection, cancer, fungal infection, infection, neutropenia, viral infection
Eur J Cancer, Vol. 33, Suppl. 4, pp. S44–S49, 1997

INTRODUCTION

PATIENTS WITH cancer are at heightened risk of infection because of their disease and its treatment. Neutropenia, the most common cause of infection, is associated with an increased risk of bacterial infection and the development of bacteraemia. Today, a broad range of antimicrobial agents, administered alone or in combination, are available for the treatment of infections due to neutropenia. Colony-stimulating factors (CSFs), immunoglobulins, granulocyte transfusions, and other cytokines may be valuable means of bolstering the weakened immune response of neutropenic patients with cancer. Trimethoprim-sulfamethoxazole and the fluoroquinolones have shown limited efficacy in antimicrobial prophylaxis, and the search continues for the optimal means of preventing infections in neutropenic cancer patients. This review summarises new and investigative approaches to the treatment of infection in cancer patients.

MICROBIOLOGICAL CONSIDERATIONS

Patients with cancer are at increased risk for infection owing to a variety of defects in host defences as a result either of their disease or its treatment (Table 1). For example, chemotherapy for leukaemia and solid tumours induces neutropenia, which is associated with an increased risk for Gram-positive and Gram-negative bacterial infections [1–3], as well as fungal infections [4–6]. Patients with myeloma and lymphocytic leukaemias may have defective B-cell function, which is associated with increased frequency of encapsulated bacterial infections, such as those due to *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*, and

Table 1. Major causes of infection in patients with cancer

Cause	Clinical situation
Neutropenia	Chemotherapy
Defective B-cell function	Myeloma and lymphocytic leukaemia
Defective chemotactic function	Hodgkin's disease
Decreased or defective T-cell function	Lymphocytic malignancies and HIV infection
Iatrogenic factors	Hospitalisation and invasive treatments

other organisms. Some patients with Hodgkin's disease have defective chemotactic function and develop a variety of bacterial infections. Patients with lymphocytic malignancies and HIV infection have decreased or defective T-cell immunity and are subject to a wide range of intracellular infections, including those caused by Mycobacteria, *Salmonella* species, *Listeria monocytogenes, Brucella* species, and *Nocardia asteroides*, as well as various herpes group viruses, fungi and protozoa, such as *Toxoplasma gondii* and *Cryptosporidium parvum* [5, 6].

Patients with cancer also are at increased risk for infection as a result of iatrogenic factors, including hospitalisation with its risk of colonisation with resistant bacteria, intravenous access devices, respiratory therapy, indwelling bladder catheters, and blood and blood-product transfusions [5, 6].

Neutropenia

Neutropenia is probably the most common host defect in patients with cancer; it is associated with an increased risk for bacterial infection as the granulocyte count approaches 500 per μl. While Gram-negative rod bacteraemia is associated with a higher mortality rate, Gram-positive coccal infections are becoming considerably more prevalent. In fact, over the past decade, Gram-positive cocci have comprised 65–70% of the isolates in neutropenic patients with single-organism bacteraemia [1–3].

The granulocyte count is not only important in predicting a risk of bacterial infection, but it is also an important prognostic feature in the recovery of patients receiving appropriate antibiotic therapy. In the first EORTC International Antimicrobial Therapy Cooperative Group (IATCG) trial, patients whose granulocyte counts rose during therapy recovered more frequently than those whose counts did not increase, or were less profoundly decreased [1].

Table 2. Some common causative bacteria in patients with neutropenic infection

Staphylococcus aureus
Streptococcus species, including *S. mitis* and other viridans streptococci
Coagulase-negative *staphylococcus*
Leuconostoc species
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Corynebacterium jeikeium
Stomatococcus mucilaginosus
Bacillus cereus
Enterococcus faecium
Stenotrophomonas (Xanthomonas) maltophila
Moraxella species
Capnocytophaga species
Legionella species
Fusobacterium nucleatum
Clostridium septicum
Mycobacterium chelonae
Bartonella henselae
Bartonella quintana

Causes of infection in neutropenic patients

Staphylococcus aureus and coagulase-negative staphylococci account for a large number of the Gram-positive cocci isolated from the blood of granulocytopenic patients with cancer (Table 2). However, *Streptococcus* species including *S. mitis* and other viridans streptococci, *Leuconostoc* species, *Corynebacterium jeikeium*, *Stomatococcus mucilaginosus*, and *Bacillus cereus* are being isolated with increasing frequency [4]. Of increasing concern is a recent report of an outbreak of vancomycin-resistant *Enterococcus faecium* (VREF) bacteraemia in an oncology unit [7]. Of 11 patients infected, 8 died despite antibiotic therapy. Risk factors for infection with VREF include gastrointestinal colonisation with the organism and prior antibiotic use. This organism is often resistant to all available bactericidal antibiotics and its occurrence in neutropenic patients presents a major therapeutic challenge.

Other infecting organisms of concern in neutropenic patients include: *Stenotrophomonas (Xanthomonas) maltophila*, which is often resistant to all antibiotics except trimethoprim-sulfamethoxazole; *Moraxella* species; *Capnocytophaga* species; *Legionella* species; *Fusobacterium nucleatum*; *Clostridium septicum*; *Mycobacterium chelonae*; *Bartonella henselae*; and *Bartonella quintana*. It is imperative that no organism isolated from a granulocytopenic patient be dismissed as a 'commensal' or non-pathogen.

Patients with neutropenia and fever may have infection in spite of negative cultures. Bacteraemia occurs in about 22% of febrile neutropenic patients. Blood cultures may be negative at the onset of fever and one of the justifications for early empirical antibiotic therapy is the hope that bacteraemic episodes can be obviated.

THERAPEUTIC CONSIDERATIONS

Fever is quite common in patients with neutropenia. About 50% of neutropenic days are spent with a fever. Although all fever is not due to infection *per se*, at least 60% of febrile episodes are associated with bacteraemia, another microbiologically documented infection, or clinically documented infection. Only approximately 20% of febrile episodes are unrelated to infection. This high rate of infection documentated in febrile neutropenic patients justifies the empirical approach to treatment that is utilised in most centres today.

Combination therapy and monotherapy

Two decades ago, most authorities felt that beta-lactam–aminoglycoside combinations were indicated in febrile neutropenic patients. Certainly, aminoglycosides alone were not

effective in these patients and the beta-lactam antibiotics available 20 or more years ago did not have as broad a spectrum as today's agents. In some early EORTC–IATCG studies [1], patients treated with carbenicillin plus gentamicin did better than those who received cephalothin plus gentamicin and those who received the two beta-lactam agents, carbenicillin plus cephalothin. In a more recent EORTC–IATCG trial, amikacin administered with ceftazidime for the entire course was more active than ceftazidime plus amikacin for only 3 days in 129 patients with documented Gram-negative rod bacteraemia [2]. This was especially true for those patients with profound and persistent neutropenia who comprise about 10% of the neutropenic population.

When aminoglycoside therapy is used today, agents usually are administered in a single daily intravenous dose. Aminoglycoside antibiotics differ from beta-lactam and other cell-wall-active antibiotics in that they share with fluoroquinolones the property of concentration-dependent killing. This means that high concentrations of drug are associated with a greater degree of bacterial killing. Clinically, if high serum levels are obtained, one can expect higher concentrations in bronchopulmonary or interstitial fluids. Transient high peak concentrations are likely to be more effective than more frequently administered lower concentrations, and may also be less nephrotoxic. Since the renal tubule cellular transport mechanism is saturable, the total accumulation of aminoglycoside within the renal tubule is actually lower with once-daily than with more frequent administration of the same total daily dose. Nephrotoxicity relates more to the concentration of drug at trough than at peak levels.

The EORTC–IATCG studied 858 febrile episodes in 677 febrile neutropenic patients who were randomised to receive amikacin (20 mg/kg, intravenously (i.v.), in a single daily dose) plus ceftriaxone (30 mg/kg, i.v., in a single daily dose), or amikacin (20 mg/kg, i.v., in three divided doses) plus ceftazidime (2 g q8h). Success rates and reasons for non-response were similar in the two groups. Nephrotoxicity, which was relatively infrequent (3% and 2%, respectively), occurred in the single daily dose group only in association with other nephrotoxic agents and occurred later than in patients receiving multiple daily doses [8].

In another recent trial, the EORTC–IATCG studied a new beta-lactamase inhibitor combination, piperacillin–tazobactam with amikacin, in comparison with ceftazidime plus amikacin [9]. In this trial, the piperacillin–tazobactam combination was more effective overall ($P = 0.05$) and in bacteraemic patients. Rash was more common in patients treated with piperacillin–tazobactam.

Also recently, this group evaluated the new carbapenem, meropenem, administered alone, compared with ceftazidime plus amikacin [10]. Similar results were obtained in both regimens, but nephrotoxicity was more frequent in ceftazidime/amikacin recipients. In a similar trial conducted by another multicentre group, De Pauw and colleagues compared ceftazidime alone with piperacillin plus tobramycin and reported similar success rates with the two regimens [11]. Adverse events were significantly lower in patients receiving monotherapy.

Other centres have compared ceftazidime with imipenem, each given as monotherapy, in febrile neutropenic patients. Freifeld and colleagues reported that similar results were obtained with each agent but that anti-anaerobic antibiotics were added more frequently to patients receiving ceftazidime, while imipenem-treated patients had more *Clostridium difficile* diarrhoea and more nausea and vomiting [12]. In another study, meropenem alone was compared directly with ceftazidime alone in febrile neutropenic patients and equivalent results were obtained, although persistent fever and antibiotic additions were more frequent in ceftazidime-treated patients [13].

Table 3. Broad-spectrum beta-lactam agents that have been reported useful for the treatment of febrile neutropenic patients when given as monotherapy or in combination with aminoglycosides

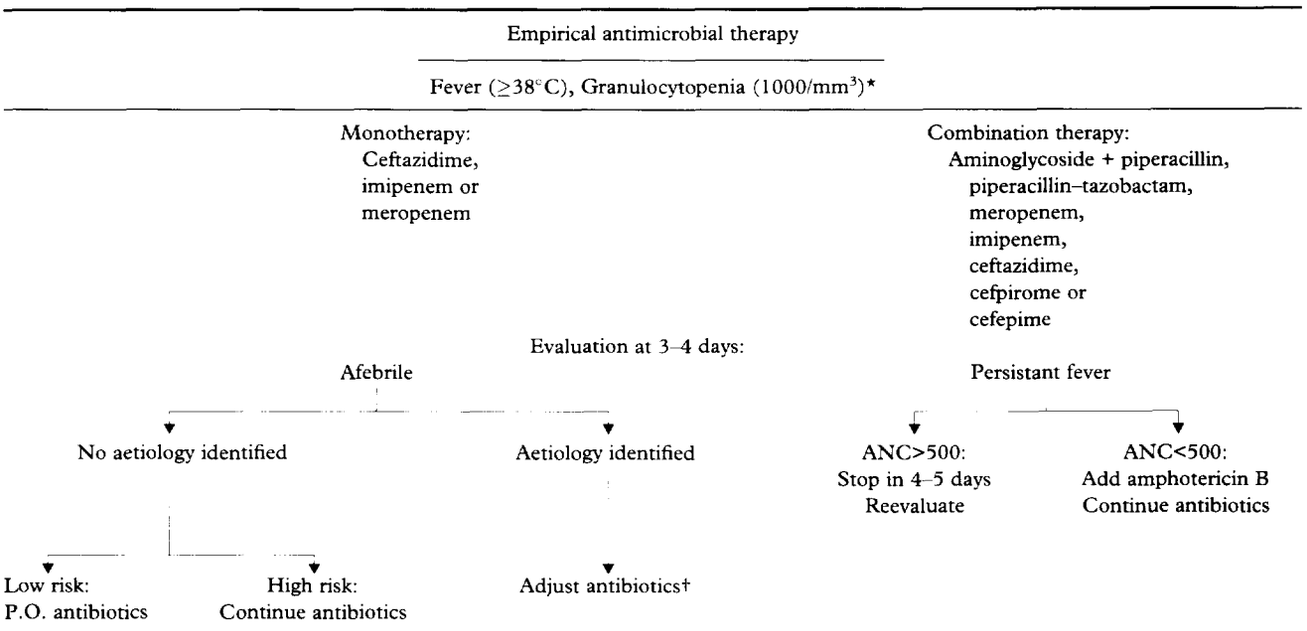
Azlocillin
Cefepime
Cefoperazone
Cefoperazone-sulbactam
Cefotaxime
Cefpirome
Ceftazidime
Ceftriaxone
Ceftizoxime
Imipenem
Meropenem
Mezlocillin
Piperacillin
Piperacillin–tazobactam
Ticarcillin–clavulanic acid

At present, there is no antibiotic or antibiotic combination of choice for the empirical treatment of febrile neutropenic patients. It is important to realise that there are many effective broad spectrum beta-lactam agents that have been reported useful in these patients, alone or in combination with aminoglycosides (Table 3). Many older agents are being rendered less useful because of increasing antibiotic resistance. Whatever agent is used for empirical therapy in febrile neutropenic patients, physicians should closely monitor the results of bacteriological tests and clinical response to modify initial therapy appropriately. Knowledge of the local patterns of antibiotic susceptibility and resistance also is crucial.

Patients are at different risks for serious infections according to their expected length of granulocytopenia [6, 14]. Patients with solid tumours whose chemotherapy renders them neutropenic for a relatively short time are at lower risk of serious infections. In these patients, a single agent such as ceftazidime, cefpirome, cefepime, imipenem, or meropenem will usually be adequate for empirical therapy. In patients with haematological malignancies whose chemotherapy renders them profoundly granulocytopenic for several weeks, the risk of serious infection, including Gram-positive and Gram-negative bacteraemia, is greater. For the latter patients, inial empirical therapy with a pseudomonas-active penicillin (such as piperacillin–tazobactam, piperacillin), an extended spectrum cephalosporin (such as cefpirome, cefepime) or a carbapenem (imipenem, meropenem) **plus** an aminoglycoside (gentamicin, tobramycin, amikacin) is recommended. The aminoglycoside can be discontinued if Gram-negative rods are not isolated from the blood within 3 or 4 days.

The inclusion of vancomycin in the initial empirical regimen is only recommended in the following cases: severe mucositis, obvious catheter-related infection, fluoroquinolone prophylaxis, or known colonisation or infection with a penicillin- or cepalosporin-resistant pneumococcus or methicillin-resistant staphylococcus. Table 4 outlines one approach to the treatment of fever in neutropenic patients. If

Table 4. Approach to treatment of fever in neutropenic patients



*See text re: empirical vancomycin; †Discontinue aminoglycoside if Gram-negative rod infection not identified. P.O., by mouth; ANC, absolute neutrophil counts.

Staphylococcus aureus or coagulase-negative staphylococcus has been isolated and the patient is failing empirical therapy, vancomycin, nafcillin, or other antibiotics to which the organism proves susceptible can be used.

Routine antiviral therapy has not been particularly well studied, but currently is not recommended for most patients with neutropenia. However, many leukaemic patients develop stomatitis or labial eruptions caused by herpes simplex virus. These patients benefit from intravenous or oral acyclovir which may prevent dissemination of herpes simplex virus to internal organs [15]. Patients undergoing bone marrow transplantation are particularly subject to cytomegalovirus infections, which might be potentially preventable with high dose acyclovir or ganciclovir [16].

NEW APPROACHES TO THERAPY IN FEBRILE NEUTROPENIC PATIENTS

Experimental approaches to the treatment of patients with febrile neutropenia include oral administration of antibiotics in an outpatient setting, use of measures to support the weakened immune response, and the administration of antimicrobial prophylactic agents.

Oral and outpatient treatment

Recently, several groups have investigated the effectiveness of oral administration of antibiotics in an outpatient setting to low-risk patients with fever and neutropenia. Patients selected for outpatient treatment should have no comorbid conditions, normal liver and renal function, have a history of good compliance with medications and should live within 30 miles of the hospital. They also should have a willing caregiver and a telephone. If patients are well selected, reasonably good success rates have been obtained with ciprofloxacin plus clindamycin or amoxicillin–clavulanate and complications of this approach have been minimal [17, 18]. Additional studies are in progress and this approach might become more common.

Bolstering the immune response

Several new approaches have been reported to support the weakened immune response in neutropenic patients with cancer (Table 5). These include adjuvant use of CSFs, immunoglobulins, granulocyte transfusions from CSF-stimulated donors, and use of other cytokines. Of these, CSFs have received the most attention. According to guidelines from the American Society of Clinical Oncology [19], CSFs are indicated for primary prophylaxis if the expected incidence of neutropenic fever is greater than 40% in the patient under consideration, and for secondary prophylaxis if the chemotherapy dose cannot be reduced to minimise infection. CSFs should not be routinely used to support standard chemotherapy regimens or outpatient chemotherapy dose intensification.

CSFs have clearly increased granulocyte counts and reduced infections in patients with cancer, but have not shown an effect in second phase induction for acute lymphocytic leukaemia [20]. Also, in acute myelogenous leukaemia (AML), CSFs have not stimulated significant regrowth of AML cells, but they also do not result in an increase in disease survival [21].

Leukapheresis following stimulation with G-CSF was performed on 35 donors at the M.D. Anderson Cancer Center, and 15 neutropenic patients with established fungal infections received a median of six granulocyte transfusions [22]. 9 of these patients showed a response to transfusions (plus continued antifungal therapy). Adverse effects occured in 6

Table 5. New approaches to bolster the immune response in neutropenic patients with cancer

Adjuvant use of colony-stimulating factors (CSFs)
Administration of immunoglobulins
Transfusion of granulocytes from CSF-stimulated donors
Administration of other cytokines

recipients and included transient dyspnea, hypoxaemia and pulmonary oedema. 2 patients had severe reactions with fever, bronchospasm, and hypoxaemia with radiological abnormalities. Although this is a preliminary report, controlled clinical trials of this approach might prove cytokine-stimulated donor granulocyte transfusions to be a useful adjunctive treatment in infected granulocytopenic patients who do not respond to antimicrobial therapy.

Antimicrobial prophylaxis

Over the past several decades, several attempts have been made to minimise bacterial infection in neutropenic patients with the use of antimicrobial prophylaxis. Although the definitive need for antibacterial prophylaxis remains unproved in large patient trials [23], it is true that non-absorbable antibiotic regimens are associated with infection reduction. However, poor compliance due to the purging effect of these regimens has limited their efficacy. More recently, trimethoprim-sulfamethoxazole has been studied and there is a definitive effect on bacterial infections in patients who comply completely with these regimens, but breakthrough Gram-negative bacteraemia does occur [24].

Fluoroquinolones have been used and are known to be effective in reducing the frequency of Gram-negative rod bacteraemia, but they have little effect on the incidence of Gram-positive infections in treated patients. The IATCG has recently published a large clinical trial of pefloxacin plus oral penicillin V (500 mg bid) or placebo as prophylactic therapy in neutropenic patients with cancer. Patients receiving the penicillin–quinolone combination showed a 50% reduction in streptococcal bacteraemias [25]. Patients with solid tumours expected to have short-term granulocytopenia probably do not need antibiotic prophylaxis, while those undergoing bone marrow transplantation do need antibacterial and antifungal prophylaxis. A recent meta-analysis suggests that fluoroquinolone prophylaxis is useful in patients with acute leukaemia [26]. However, caution is raised about the potential for antibiotic-resistant streptococci as well as Gram-negative bacteria in the face of extensive use of prophylactic antibiotics in these patients. It is likely that a search for the optimal prophylactic approach to preventing infections in granulocytopenic cancer patients will continue as we wait for the 'ideal' antibiotic to be introduced.

CONCLUSION

Recent changes in microbial ecology and microbial resistance patterns have emphasised the need for continual reassessment of antimicrobial therapy in cancer patients with neutropenic infection. Recently, amikacin has shown benefit in combination with ceftazidime, ceftriaxone, and piperacillin–tazobactam. Meropenem, administered as monotherapy, has demonstrated efficacy in patients with febrile neutropenia and also has a good safety profile. But despite the promise of these and other new compounds, there is still no antibiotic or antibiotic combination of choice for the empirical treatment of febrile neutropenia.

Various investigational approaches may prove to be beneficial in the management of patients with fever and neutropenia. Outpatient treatment with oral antibiotics appears to be a feasible alternative to hospitalisation for many low-risk patients. Various agents, including CSFs, immunoglobulins, transfused granulocytes, and other cytokines may be valuable in bolstering patients' weakened immune responses. Trimethoprim-sulfamethoxazole and fluoroquinolones have shown efficacy in antimicrobial prophylaxis, and the search continues for the optimal prophylactic approach to preventing infections in neutropenic cancer patients.

1. The EORTC International Antimicrobial Therapy Project Group. Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. *J Infect Dis* 1978, **137**, 14–29.
2. Calandra T, Klastersky J, Gaya H, Glauser MP, Meunier F, Zinner SH. EORTC International Antimicrobial Therapy Cooperative Group. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med* 1987, **317**, 1692–1698.
3. EORTC International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada—Clinical Trials Group. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991, **35**, 873–878.
4. Zinner SH. New and unusual infections in neutropenic patients. In Klastersky J, ed. *Infectious Complications of Cancer.* Boston, Kluwer, 1995, 173–184.
5. Zinner SH. Treatment and prevention of infection in immunocompromised hosts. In Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases.* Philadelphia, W.B. Saunders, 1992, 1057–1064.
6. Glauser MP, Zinner SH. Mechanisms of the acquisition of bacterial infections in cancer patients. In Klastersky J, ed. *Infection in Cancer Patients.* New York, Raven Press, 1982, 13–24.
7. Edmond MB, Ober JF, Weinbaum DL, *et al.* Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin Infect Dis* 1995, **20**, 1126–1133.
8. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. *Ann Intern Med* 1993, **119**, 584–593.
9. Cometta A, Zinner S, deBock R, *et al.* Piperacillin–tazobactam versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother* 1995, **39**, 445–452.
10. Cometta A, Calandra T, Gaya H, *et al.* Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother* 1996, **40**, 1108–1115.
11. De Pauw BE, Deresinski SC, Feld R, Lane-Allman EF, Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer: a multicenter randomized trial. *Ann Intern Med* 1994, **120**, 834–844.
12. Freifeld AG, Walsh T, Marshall D, *et al.* Monotherapy for fever and neutropenia in cancer patient: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* 1995, **13**, 165–176.
13. Meropenem Study Group of Leuven, London and Nijmegen. Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. *J Antimicrob Chemother* 1995, **36**, 185–200.
14. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two center validation of a prediction rule. *J Clin Oncol* 1992, **10**, 316–322.
15. Whitley RJ, Gnann JW Jr. Acyclovir: a decade later. *N Engl J Med* 1992, **327**, 782–789.
16. Schmidt GM, Horak DA, Niland JC, *et al.* A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. *N Engl J Med* 1991, **324**, 1005–1011.
17. Talcott JA, Whalen JC, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a

pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol* 1994, **12**, 107–114.
18. Rubenstein E, Rolston K. Outpatient management of febrile episodes in neutropenic cancer patients. *Support Care Cancer* 1994, **2**, 369–373.
19. Anon. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony stimlating factors: evidence based, clinical practice guidelines. *J Clin Oncol* 1994, **12**, 2471–2508.
20. Dibenedetto SP, Ragusa R, Ippolito AM, *et al.* Assessment of the value of treatment with granulocyte colony-stimulating factor in children with acute lymphoblastic leukaemia: a randomized clinical trial. *Eur J Haematol* 1995, **55**, 93–96.
21. Stone RM, Berg DT, George SL, *et al.* Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. *N Engl J Med* 1995, **332**, 1671–1677.
22. Hester JP, Dignani MC, Anaissie EJ, Kantarjian HM, O'Brien S, Freireich EJ. Collection and transfusion of granulocyte concentrates from donors primed with granulocyte stimulating factor and response of myelosuppressed patients with established infection. *J Clin Apheresis* 1995, **10**, 188–193.
23. Zinner SH. Prophylactic uses of fluoroquinolone antibiotics. *Infect Dis in Clin Practice* 1994, **3**(Suppl 3), S203–S210.
24. EORTC International Antimicrobial Therapy Group. Trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients. *J Infect Dis* 1984, **150**, 372–379.
25. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (Writing Committee: Zinner S, Calandra T, Meunier F, Gaya H, Viscoli C, Klastersky J, Glauser MP, Langenaeken J, and Paesmans M). Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer. A trial of oral penicillin V or placebo combined with pefloxacin. *JAMA* 1994, **272**, 1183–1189.
26. Cruciani M, Rampazzo R, Malena M, *et al.* Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996, **23**, 795–805.