Antimicrobial regimens prescribed by Canadian physicians for chemotherapy-induced febrile neutropenic episodes

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OBJECTIVE: To study the antimicrobial management of cancer patients with chemotherapy-induced neutropenia by Canadian physicians.

SETTING: A cohort of 274 cancer patients with severe neutropenia (ie, less than 0.5×10^9 neutrophils/L) who participated in a prospective double-blind, placebo controlled study on antifungal prophylaxis conducted in 14 Canadian university-affiliated centres. Antifungal prophylaxis (oral fluconazole 400 mg daily) was administered to 153 of 274 (56%) patients.

RESULTS: Antibacterial prophylaxis with a quinolone was given to 87 patients (32%) at the onset of chemotherapy whereas trimethoprim/sulphamethoxazole was given to 56 (20%) patients. Fever (ie, 38°C or over) occurred in 216 (79%) patients after a median duration of neutropenia of four days (range one to 31 days). Empirical antibacterial antibiotics were administered in 214 febrile patients. In 164 (77%) patients antibiotics were started during the first 24 h of fever. Monotherapy with a third generation cephalosporin and duotherapy with a antipseudomonal beta-lactam and an aminoglycoside were prescribed in 69 (32%) and 61 (28%) of the febrile patients, respectively. Inclusion of vancomycin in the initial empirical regimen was noted in 32 (15%) patients. Modifications of the initial regimen occurred in 187 (87%) pa-

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tients after a median of five days (range one to 28 days). Empirical systemic amphotericin B was added after a median duration of nine days (range one to 34 days) of the empirical antibacterial regimen.
CONCLUSIONS: Overall, the antimicrobial management of cancer patients with chemotherapy-induced neutropenia by Canadian physicians follows the current guidelines promulgated by the Infectious Diseases Society of America.

Key Words: *Antimicrobial management; Cancer patients; Febrile neutropenia*

Antibiothérapie prescrites par les médecins canadiens pour des épisodes de neutropénie fébrile induits par la chimiothérapie

OBJECTIF : Étudier le mode de traitement antimicrobien administré par les médecins canadiens dans les cas de neutropénie induite par la chimiothérapie chez les patients cancéreux.
CONTEXTE : Une cohorte de 274 patients cancéreux atteints de neutropénie grave (c.-à-d. moins de 0,5 x 10^9 neutrophiles/L) qui ont participé à une étude prospective à double insu avec témoins sous placebo, portant sur une prophylaxie antifongique et menée dans 14 centres universitaires canadiens. La prophylaxie antifongique (fluconazole oral, 400 mg par jour) a été administrée à 153 patients sur 274 (56 %).
RÉSULTATS : L'antibioprophylaxie par quinolone a été administrée à 87 patients (32 %) dès le début de la chimiothérapie, alors que du trimétoprime/sulfaméthoxazole a été administré à 56 patients (20 %). La fièvre (38 °C ou plus) est apparue chez 216 patients (79 %) après que la neutropénie ait en moyenne duré quatre jours (entre 1 et 31 jours). L'antibiothérapie empirique a été administrée à 214 patients fébriles. Chez 164 patients (77 %) les antibiotiques ont été débutés dès les quatre premières heures de fièvre. La monothérapie au moyen d'une céphalosporine de troisième génération et la bithérapie au moyen d'une bêtalactamine antipseudomonas et d'un aminoglycoside a été prescrite à 69 (32 %) et 61 (28 %) des patients fébriles respectivement. L'inclusion de vancomycine dans le schéma empirique initial a été notée chez 32 patients (15 %). Des modifications du schéma initial ont été apportées chez 187 patients (87 %) après une moyenne de cinq jours (de 1 à 28 jours). L'amphotéricine B systémique a été ajoutée empiriquement après une durée moyenne de neuf jours (entre 1 et 34 jours) d'une antibiothérapie empirique.
CONCLUSIONS : De façon globale, chez les patients cancéreux atteints de neutropénie induite par la chimiothérapie, l'antibiothérapie prescrite par les médecins canadiens est fidèle aux directives actuelles préconisées par l'*Infectious Disease Society of America*.

Over the past three decades, important advances in biomedical and pharmacological technology have had a dramatic impact on the care of patients with malignancies. Antibiotics have significantly improved the outlook for cancer patients. Improved preventive and therapeutic strategies for infections have contributed to reduce the morbidity and mortality observed in severely immunocompromised patients (1). Recommendations on the initial selection and subsequent management of empirical antibiotics in profoundly neutropenic patients with unexplained fever have been written and recently updated (2). Although these recommendations, based on scientific publications and peer reviewed information, are general and must be applied wisely with respect to individual situations, adherence to them has rarely been evaluated. We have recently conducted a prospective double-blind, placebo controlled study on antifungal prophylaxis in 14 Canadian university-affiliated centres (3). In this study's protocol, there were provisions for antibiotic management, but physicians were permitted to apply their own centres' usual standard of care. We, therefore, had the opportunity to monitor the use of antimicrobial agents in cancer patients with unexplained fever and report an observational study on the antimicrobial management of cancer patients with chemotherapy-induced neutropenia by Canadian physicians.

PATIENTS AND METHODS

This was a descriptive study on the use of antimicrobial agents in a cohort of severely neutropenic patients who participated in a prospective double-blind, placebo controlled study on antifungal prophylaxis. The use of antibiotics was assessed from the induction of chemotherapy to the initiation of parenteral antifungal agents (amphotericin B [Fungizone, Bristol-Myers Squibb Canada Inc, Montreal, Quebec]). Eligible patients were to undergo cytotoxic chemotherapy for acute leukemia or conditioning therapy for autologous bone marrow transplantation (aBMT). Patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) undergoing remission induction, reinduction therapy after primary relapse or postremission consolidation therapy, and patients undergoing aBMT were included if they were expected to remain neutropenic (less than 0.5×10^9 neutrophils/L) for more than seven days. Occurrence of fever (38.0°C or greater) related to the onset of neutropenia, and the use of antimicrobial agents for prophylaxis and treatment of febrile neutropenia were recorded.

RESULTS

The clinical characteristics of the 274 evaluable patients are shown in Table 1. The study was conducted during a 23-month period (January 1994 to November 1995). Antifungal prophylaxis (oral fluconazole, 400 mg once daily) was administered to 153 (56%) patients according to the drug randomization protocol. Antibacterial prophylaxis was added at the onset of chemotherapy at the attending physicians' discretion. In 87 (32%) patients, a quinolone was used, whereas trimethoprim/sulphamethoxazole was used in 56 (20%) patients. Fever occurred in 216 (79%) patients (Figure 1) after a median of 9.5 days (range zero to 42 days) following the first day of chemotherapy and a median of three days (range one to 31 days) following the onset of neutropenia. Among the 216 patients

TABLE 1
Characteristics of the 274 evaluable patients

Characteristic	Value
Sex (male to female)	141:133
Age (median years, range)	46.4 (17-80)
Underlying illness	
Acute myeloid leukemia	128
Acute lymphocytic leukemia	26
Autologous BMT	120
Acute myeloid leukemia	8
Acute lymphocytic leukemia	2
Non-Hodgkin's lymphoma	58
Hodgkin's disease	28
Solid tumour	24
Cytotoxic regimens	
Acute lymphoblastic leukemia-type regimens	21
Mitoxantrone + etoposide	17
Cytarabine + anthracycline	85
HDARA-C based regimens	31
Autologus BMT conditioning	120
Antifungal prophylaxis (%)	153 (56)
Documented infections (%)	145 (53)
Bacterial	119
Fungal	26

BMT Bone marrow transplant

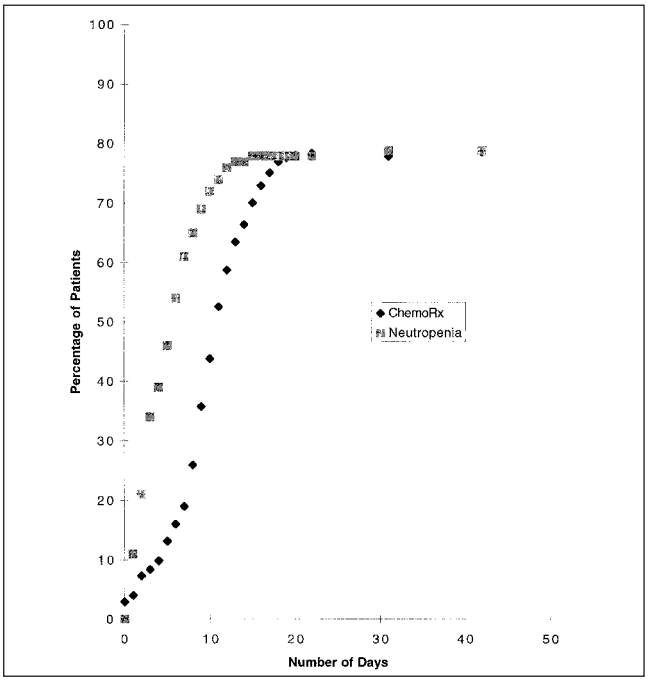

Figure 1) *Proportion of febrile patients relative to the first day of chemotherapy and the first day of neutropenia*

who became febrile, 50 (23%) received a quinolone and 46 (21%) trimethoprim/sulphamethoxazole. Febrile neutropenia occurred in 100 of 120 aBMT (83%, 95% CI 77% to 90%) compared with 116 of 154 non-BMT patients (75%, 95% CI 69% to 82%). The 95% CI for the difference between the aBMT and non-BMT patients was –1.5% to 17.5% (P=0.144, not significant). Empirical antibacterial antibiotics were administered in 214 febrile patients. In 164 (77%) patients, antibiotics were started during the first 24 h of fever and in 91% after 48 h of fever. Monotherapy with a third generation cephalosporin or a carbapenem and duotherapy with a antipseudomonal betalactam and an aminoglycoside were prescribed to 69 (32%), five (2%) and 61 (28%) febrile patients, respectively (Table 2). Vancomycin was included in the initial empirical regimen in 32 (15%) patients. The first modifications of the initial regimen occurred in 187 (87%) patients after a median of five days (range one to 28 days) (Figure 2). Systemic amphotericin B was added to the antibacterial regimen in 102 of the 214 (48%) patients (Figure 3). Its addition occurred after a median of nine days of empirical antibiotics and 13 days after the first day of cytotoxic therapy. A total of 18 patients (6.5%) died during the study.

TABLE 2
Selected initial courses of empirical antibiotics

Therapy type	Number of patients
Monotherapy	90 (42%)
Third generation cephalosporins	69
Penicillins	5
Carbapenems	5
Aminoglycosides	4
First generation cephalosporins	3
Glycopeptides	2
Quinolones	2
Combination therapy	124 (58%)
Double therapy	86
Antipseudo penicillins + aminoglycosides	42
Antipseudo cephalosporins + aminoglycosides	19
Other cephalosporins + aminoglycosides	4
Cephalosporins + glycopeptides	10
Others	11
Triple therapy	34
Penicillins + aminoglycosides + cephalosporins	10
Penicillins + aminoglycosides + glycopeptides	7
Penicillins + glycopeptides + antianaerobes	4
Cephalosporins + glycopeptides + aminoglycosides	2
Others	11
Triple therapy	4
Total	214

DISCUSSION

The management of infection in neutropenic patients requires careful decision-making. Since the early 1970s, prompt empirical antimicrobial therapy has been advocated as a way to treat febrile episodes in neutropenic patients with cancer (4). Our observations show that, in general, the participating physicians in our study used prompt empirical antibacterial therapy. Empirical antibiotics were given to 99% of our febrile neutropenic patients, and, in 77% of these febrile patients, antimicrobial agents were started during the first 24 h of fever.

Antimicrobial regimens available for the treatment of febrile episodes in neutropenic cancer patients initially were recently reviewed by the Infectious Diseases Society of America's expert panel (2). There is a general consensus that when the etiology is unknown, there are very little differences between monotherapy and multidrug combinations in the treat-

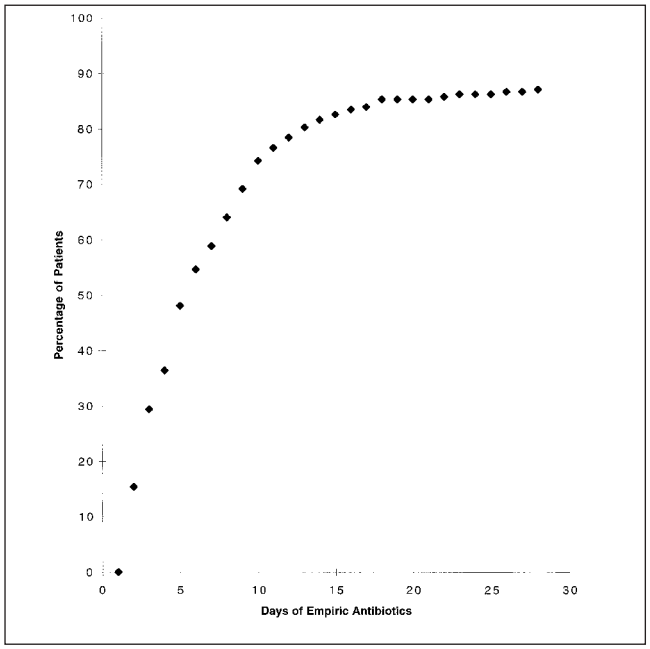

Figure 2) *Time to the first modification of the antimicrobial regimen relative to the first day of empirical antibiotics*

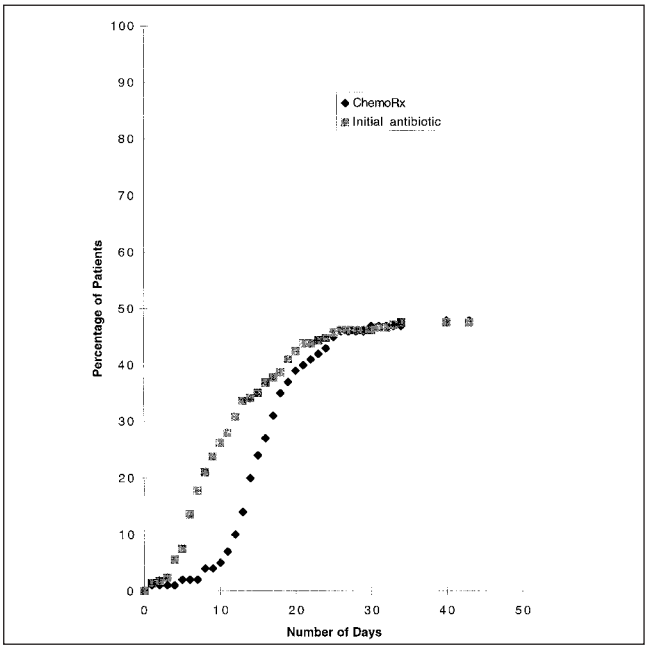

Figure 3) *Administration of amphotericine B relative to the first day of chemotherapy and onset of empirical initial antibiotics*

ment of uncomplicated episodes of fever in neutropenic patients. Third generation cephalosporins (ceftazidime or cefepime) or a carbapenem (imipenem/cilastatin or meropenem) can be considered standards of monotherapy, whereas antipseudomonal cephalosporins or penicillins combined with aminoglycosides represent usual combination therapy (5-7). In this population of patients, monotherapy was used in 90 of 214 (42%) patients, with ceftazidime or imipenem selected 77% of the time. Combination therapy was used in more than half (58%) of the patient population. In most cases, antipseudomonas cephalosporins or penicillins combined with aminoglycosides were used. Such combinations have the advantage to be potentially synergistic against some Gram-negative bacilli (8), and may also prevent emergence of resistance during treatment (9,10).

Vancomycin was included in the initial empirical regimen by our attending physicians in 32 of 214 (15%) patients. Controversy surrounds whether vancomycin should be part of the initial antimicrobial regimen in febrile neutropenic patients. Emerging resistance of enterococci to vancomycin and failure to improve the overall mortality associated with Gram-positive infections have been the major arguments against systematically adding vancomycin to the initial empirical regimen. However, at times, it is warranted because some Gram-positive infection, particularly viridans streptococcal infections, may be fulminant and associated with a high mortality (11). To reduce the excessive use of vancomycin and to prevent the spread of vancomycin resistance, it is recommended that institutions with a low incidence of fulminant Gram-positive infections avoid using vancomycin systematically as part of the initial antimicrobial regimen in febrile neutropenia (12). However, it would be prudent to include vancomycin in the regimen of selected patients with the following: serious catheter-related infections (13); intensive chemotherapy that causes substantial mucosal damage such as high dose cytarabine; hypotension or other evidence of cardiovascular impairment; Gram-positive blood stream infection before final identification and susceptibility testing; colonization with penicillin-resistant pneumococci or methicillin-resistant staphylococci and in patients who have received quinolone prophylaxis.

Antibiotic strategy, after the empirical phase often requires modification if fever persists. In our observations, modification of the antibiotic regimens was documented in 87% of our patient population, with the first modification occurring after a median of five days (range one to 28 days) of antibiotic therapy. This is in keeping with previous reports that the time-to-defervescence for febrile neutropenic patients who receive antibiotic regimen was two to seven days (median time five days) (14). Therefore, at least three days of antibiotic treatment are usually required to determine the efficacy in clinically stable patients.

There is no consensus on the optimal timing for addition of amphotericin B in persistently febrile neutropenic patients despite the administration of broad-spectrum antibiotics in adequate dosage. Most experts agree that, after one week of profound neutropenia and fever, the addition of systemic antifungal is warranted due to the increased incidence of candida and aspergillus infections in this patient population (15). Amphotericin B remains the preferred selection in such situations. In our study, amphotericin B was added to the antibacterial regimen in 102 of 214 (48%) initially febrile patients. Although approximately half of our cohort of patients received prophylactic fluconazole, it proved no more successful than placebo in obviating the need for parenteral amphotericin B (3).

CONCLUSIONS

Overall, the antimicrobial management of cancer patients with chemotherapy-induced neutropenia by Canadian physi-

cians follows the current suggested guidelines to treat febrile patients promptly with broad-spectrum antibiotics, avoid the systematic addition of vancomycin in the initial regimen and allow, in clinically stable patients, two to seven days before modifying the initial regimen.

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