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Comments and Critique

Outpatient Treatment of Febrile Neutropenic Patients with Cancer

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For many decades, fever has been the leading cause of morbidity and mortality in patients receiving myelosuppressive, antineoplastic therapy [1]. Until recently, all febrile neutropenic patients were hospitalised for the administration of empiric, broad spectrum, intravenous antibiotic therapy [2]. This approach was considered necessary because a substantial number of febrile episodes in neutropenic patients are caused by bacterial pathogens, and are associated with an unacceptable risk of complications, including septic shock and death, in the first few days after the onset of fever, unless treated promptly and aggressively [3]. However, patients with fever and neutropenia are not a homogeneous population, and not all such patients have the same risk of developing serious complications or of dying. The standard practice of hospitalising all febrile neutropenic patients for antiobiotic therapy has become an important research question particularly in the current health care environment, where cost and health-related outcomes are being evaluated.

RISK STRATIFICATION

The outcome of neutropenic patients with fever of undetermined origin (FUO) was strongly influenced by both the depth and the duration of neutropenia in a study from the National Cancer Institute [4]. Patients with ≤7 days of neutropenia had response rates to initial antimicrobial therapy of 95% compared to only 32% in patients with >2 weeks of neutropenia. Many studies have also demonstrated significantly better response rates in patients with documented infections in whom recovery from neutropenia occurs, compared with patients with persistent neutropenia [5–7]. The work of Talcott and colleagues has led to the recognition of well defined risk groups among febrile neutropenic patients [8,9]. They have categorised patients into four groups based on clinical criteria that can be assessed within 24 h after the onset of the febrile episode. Group 1 consisted of patients who were hospitalised when they developed febrile neutropenia. This group had substantial morbidity and a mortality rate of 13%. Group 2 included outpatients with concurrent comorbidity (hypotension, altered mentation, respiratory failure, uncontrolled bleeding, dehydration, uncontrolled pain, hypercalcaemia, cord compression, etc.) Serious complications occurred in 40% of these patients and 12% died. Group 3 consisted of outpatients without comorbidity, but with progressive uncontrolled cancer. Serious complications occurred in 25% of these patients and 18% died. Group 4 included clinically stable outpatients (responsive tumours and no comorbidity) who rarely developed serious complications (3%) and in whom no mortality occurred ($P=<0.0001$ for Group 4 versus Groups 1–3.

Based upon their risk assessment model, Talcott and associates performed a pilot study of early discharge to home antibiotic therapy among low-risk (Group 4) febrile neutropenic patients [10]. In order to further reduce risk, they excluded Group 4 patients who had significant infections (pneumonia, bacteraemia or urinary tract infection) or were 65 years of age or older. Eligible patients received broad spectrum intravenous antibiotics in the hospital. The initial regimens used were either mezlocillin plus gentamicin or ceftazidime as a single agent, with therapeutic alterations being made as needed by the patients' primary physicians. After 2 days of in-hospital observation, patients were enrolled in the home intravenous antibiotic programme. The mean duration of neutropenia among the 30 patients treated in this manner was 6 days (however, 5 patients had neutropenia of 13–36 days duration). Only 5 (17%) had clinically documented infections (4 had cellulitis; 1 had a suspected dental abscess). Patients were treated at home for a median of 3.5 days (range 1–24 days). Only 16 (53%) responded to the initial antibiotic regimen. Four developed serious medical complications (hypotension, acute renal failure, disseminated mucor infection, coagulase negative staphylococcal bacteraemia secondary to a contaminated platelet transfusion) and required prolonged re-admission. Five were re-admitted for persistent fever, and 5 received additional antibiotics at home. Although no patients died, the high rate of re-admission (30%) and alteration of the original antimicrobial regimen raises questions about the practical applications of Talcott's prediction model. Perhaps an over-representation of patients with acute leukaemia and/or persistent neutropenia of >7 days accounts for the results of their pilot study. Consideration of the expected duration of

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severe neutropenia and the patients' underlying neoplasm (that is, leukaemia or solid tumour) might further refine the prediction model, and lead to better patient selection and a higher success rate.

Recently, Gilbert and associates have described a programme of sequential prophylactic oral antiobiotics with ciprofloxacin and rifampin followed by once daily parenteral vancomycin plus tobramycin and oral ciprofloxacin for the treatment of febrile neutropenic episodes in patients who have undergone autologous bone marrow transplantation [11]. Their strategy reduced the incidence of documented infections and virtually eliminated documented bacteraemias. Although this patient population is recognised as having a prolonged expected duration of neutropenia and should be at high risk of developing complications, the strategy employed by these investigators was successful and facilitated early discharge from the hospital to the outpatient setting.

Malik and colleagues reported the use oral ofloxacin alone compared with parenteral amikacin plus either carbenicillin, cloxacillin, or piperacillin for empiric in-patient treatment of febrile episodes in neutropenic cancer patients. In their study, more than half the patients had leukaemia or lymphoma, and the mean duration of neutropenia was 9 days. The response rates for oral ofloxacin and for the parenteral combination were identical (53%). Four pateints on the oral arm died (7%) whereas 6 patients on the intraveneous regimen died (10%) [12]. Demonstrating equal efficacy between oral and intraveneous therapy has major implications for management of febrile neutropenic patients in countries such as theirs (Pakistan), where resources are limited. Nevertheless, their study is limited because these patients were all in-patients and it is not clear which subset would safely benefit from outpatient oral therapy. In a follow-up study [13], 111 patients who lived far from the oncology centre were instructed to take oral ofloxacin at the onset of fever during their period of neutropenia ($<0.5 \times 10^9$/l). Follow-up was maintained by daily telephone contact, and 83% of the episodes were successfully managed by this method without hospitalisation. Two patients died at home and 17 (15%) did not respond to ofloxacin, requiring hospitalisation.

EXPERIENCE FROM THE M.D. ANDERSON CANCER CENTER

For the past 6 years, the Ambulatory and Supportive Care Oncology Research Programme (ASCORP) of the University of Texas, M.D. Anderson Cancer Center has been developing and refining a practical approach to the initial identification and successful management of low-risk febrile, neutropenic patients with cancer, using a total outpatient strategy. We have independently developed reproducible criteria allowing us to identify low-risk subsets of patients who benefit from outpatient oral and intravenous antibiotic regimens. Patients are identified at the time of presentation to our Ambulatory Treatment Center, and risk stratification is done after a thorough history, physical and standardised diagnostic evaluation. Low-risk patients who are febrile and neutropenic are those who do not have comorbidity requiring hospitalisation. Specific medical exclusion criteria include the presence of hypotension, systolic blood pressure <90/mm Hg tachypnoea (respiratory rate >30/min), altered sensorium, renal insufficiency (serum creatine >2.5 mg/dl or creatine clearance <50 ml/min), uncontrolled hypercalcaemia, hyponatraemia (serum sodium <128 mg/dl or abnormal transamines (>4 × normal). Patients must stay within a 30 mile radius of the cancer centre and have a history of compliance with prior medical therapy, a telephone in their residence, and demonstrate an ability to manage their care alone or have a willing caregiver accept the responsibility.

In our original trial (ASCORP-I), we compared an intravenous regimen (aztreonam plus clindamycin to an oral regimen (ciprofloxacin plus clindamycin) in low-risk febrile neutropenic patients, who after an initial period of observation of 8 h in our Ambulatory Treatment Center, were treated without hospitalisation [14]. Twenty-six per cent of patients had haematological malignancies and 93% were moderately or severely neutropenic (<500 neutrophils/mm^3) when enrolled on the study. Thirty-nine per cent had documented infections, of which 88% were microbiologically documented including bacteraemias, urinary tract infections, and other skin/soft tissue infections. Patients above 65 years of age were not excluded, if otherwise eligible. Response rates for both regimens were much higher than those obtained in the study by Talcott and colleagues. The intravenous regimen was associated with a response rate of 95% and the oral regimen with a response rate of 88% ($P=0.19$), giving a combined response rate of 92% for outpatient antibiotic therapy. The oral regimen was associated with renal toxicity, and combining safety and efficacy, the intravenous regimen was superior. Of the 83 episodes, only 6 required admission to the hosptial, 3 for management of renal toxicity and 3 for treatment of persistent fever. There were no infection-related complications such as septic shock, and no infection-related deaths among patients on this trial. Although patients with solid tumours may have been over-represented in this trial compared to Talcott's pilot study, the high response rates seen with both initial regimens and the low rate of re-admission (7%) substantiates the practical application of our model of eligibility for outpatient management.

In our second and recently completed trial (ASCORP-II), we retained the intravenous regimen (aztreonam plus clindamycin) but changed the oral regimen to ciprofloxacin plus amoxicillin/clavulanate. We also reduced the dosage or oral ciprofloxacin from 750 mg to 500 mg three times daily [15]. Interim analysis confirm the experience of ASCORP-I. The oral regimen has an 88% response rate whereas with the intravenous regimen the response rate is 90%, with a combined rate of 89% for outpatient antibiotic therapy. As in the previous study, the majority (90%) of patients were moderately to severely neutropenic and had underlying solid tumours. A high proportion (55%) had documented infections indicating that, with careful patient selection and appropriate antimicrobial therapy, ambulatory antibiotic therapy in low-risk febrile, neutropenia need not be confined to patients with FUO. As in the first trial, no complications or infectious deaths have occurred, and in this study, no nephrotoxicity has been seen in patients on either regimen.

FUTURE DIRECTIONS FOR RESEARCH

Based upon the success of our eligibility criteria and treatment strategies, patients with solid tumours and no comorbidity, who have an expected duration of neutropenia <7 days, can have their febrile episode managed successfully in the outpatient setting 90–95% of the time. Patients with lymphoma or leukaemia or those who have an expected duration of neutropenia >7 days should probably start treatment for their febrile episode in the hospital. Early discharge criteria must then be systematically studied in controlled clinical trials in order to test the safety and efficacy of outpatient management for these moderate to high-risk febrile neutropenic patients. Perhaps sequential

antibiotic strategies such as therapeutic intravenous antibiotics, followed by an early switch to oral antibiotics for responders will prove to be a cost-effective management strategy for moderate to high-risk febrile neutropenic patients. The quinolones appear to be ideal agents for such testing.

We do not yet know the role of growth factors in the setting of febrile neutropenia. The recent work by Maher and colleagues demonstrated a 1 day reduction in the median duration of neutropenia (4 to 3 days) as well as time to resolution of febrile neutropenia (6 to 5 days) but not total days of fever [16]. Consequently, the cost-effectiveness of filgrastim (G-CSF) as an adjunct to antibiotic therapy in this setting is an important area of study.

Patients with prolonged duration of neutropenia such as those undergoing high-dose chemotherapy and stem cell support, should be good candidates for clinical trials with prophylactic and therapeutic antibiotic regimens as Gilbert and associates have reported. Other antibiotic combinations may prove to be safe and effective in this group, and controlled trials demonstrating the cost-effectiveness of such strategies are needed.

Finally, it is time to study the low-risk group and ask whether low-risk neutropenic patients with fever of undetermined origin can be treated with antibiotics for a short course of therapy (3 or 4 days), regardless of neutrophil count, without a deleterious effect on their outcome. We believe that these questions can only be addressed through well designed clinical trials, and the conduct of such studies in the ambulatory setting is challenging yet rewarding for clinical investigators.

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