The Outpatient Management of Febrile Neutropenia in Cancer Patients

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Treatment of fever and neutropenia in cancer patients has been recognized for 30 years as a medical emergency, requiring prompt in-hospital evaluation and institution of broad-spectrum intravenous (IV) antibiotics. This action

Introduction

A decade ago, it was inconceivable that febrile neutropenic cancer patients could be treated anywhere other than the inpatient hospital setting. This tradition of hospital-based, parenteral antibiotic therapy evolved from a series of studies describing the natural history of fever in cancer patients. Thirty years ago Bodey and colleagues demonstrated that the risk of infectious complications in cancer patients undergoing chemotherapy was directly related to the depth and duration of ensuing granulocytopenia. A particularly dramatic increase in serious infections was noted to occur at a granulocyte count of < 500 cells/mm³, rendering that count a benchmark of risk in the cancer patient population [1].

Later studies determined that neutropenic patients with potentially life-threatening bacteremias could not be readily distinguished, on the basis of presenting characteristics, from those with less significant infections (ie, urinary tract or minor viral infections) [2]. Fever alone appeared to be the most reliable indicator of a serious bacterial infection in the neutropenic patient. A substantial proportion of febrile episodes were associated with invasive bacterial infections. Withholding antibiotic therapy in febrile neutropenic patients, even for 1 or 2 days until culture results were available, was found to be a costly delay: Mortality from untreated gram-negative sepsis was approximately 80% [3].

The consequence of these early findings was that any patient presenting with fever during neutropenia was considered to be at high risk for a life-threatening infection and deserving of hospital admission for prompt delivery of empiric broad-spectrum intravenous (IV) antibiotics, procurement of appropriate microbiologic cultures, and close clinical monitoring throughout the neutropenic period, until the granulocyte count returned to 500 cells/mm³ or higher. This approach has become a standard of care, associated with survival rates > 95% for neutropenic episodes [4]. What, then, now permits us to contemplate the option of outpatient antibiotic therapy for febrile neutropenic patients? Although the economic and political forces that are driving changes in health-care delivery and reimbursement provide clear incentives to seek less expensive alternatives to inpatient care for many illnesses, it is important also to consider current care standards in a historical context. The stringent recommendations for management of febrile neutropenia were derived from observations made nearly three decades ago, primarily in patients undergoing intensive therapy for acute leukemia. These recommendations were applied broadly to all patients with fever and neutropenia, however, regardless of underlying cancer, type of chemotherapy, clinical status, or other medical conditions.

Until recently, it has been assumed that all cancer patients with neutropenia share equal risk for serious infectious complications when they become febrile. In recent years, however, there has been an evolution in the types of chemotherapeutic strategies and supportive-care approaches available for cancer patients. Moreover, there have been significant changes in the spectrum and character of infections that affect the neutropenic cancer patient. All of these changes have led to an increasing awareness that not all patients with fever and neutropenia are equal.

Changing Features of Fever and Neutropenia

Emergence of Gram-Positive Pathogens

During the 1960s and '70s, gram-negative bacteremia was a common cause of fever and infectious
mortality in neutropenic cancer patients. However, the incidence of severe gram-negative infections decreased dramatically between the late 1970s and the early ‘80s, with gram-positive organisms becoming the most commonly isolated pathogens from preantibiotic blood cultures in most centers [5].

In a series of large studies performed by the European Organization for Research and Treatment of Cancer (EORTC) over the last decade, the proportion of bloodstream isolates from neutropenic patients that were gram-negative organisms declined progressively, from 71% in the mid-1970s to 31% in the late ‘80s [6-8]. In particular, *Pseudomonas aeruginosa*, which once accounted for the majority of gram-negative isolates and was associated with high mortality, is now a relatively rare entity. At the National Cancer Institute (NCI), for example, fewer than 10 cases of primary *P. aeruginosa* bacteremia have been recognized during the past decade, among more than 800 episodes of fever and neutropenia.

Recent data from a number of clinical trials indicate that at least 60% of bacteremic episodes among febrile neutropenic patients are due to gram-positive organisms [8-11]. This trend may be related to the widespread use of in-dwelling central venous catheters and to fluoroquinolone prophylaxis, as the available fluoroquinolones lack reliable activity against many gram-positive species and may select for them as pathogens. Coagulase-negative staphylococci, *Staphylococcus aureus*, streptococci, enterococci, and even corynebacteria are among the more common organisms responsible for infection and are generally associated with a lower incidence of morbidity and mortality than gram-negative pathogens. There is ample evidence that, unlike the experience with gram-negative bacteremias, specific therapy against gram-positive pathogens (eg, vancomycin) need not be a component of the initial empiric antibiotic regimen, but rather, can be safely delayed until the return of blood culture results and identification of the organism, often a matter of 24 to 48 hours after presentation [9,12-14].

**Decline in Incidence of Infections**

In addition to changes in the types of infections seen, the overall incidence of documented infections has decreased, with a greater proportion of neutropenic patients having no identifiable cause of their fever (ie, fever of unknown origin). Over two-thirds of febrile neutropenic patients studied at the NCI in the past decade had fever of unknown origin, whereas in the 1970s and early ‘80s, between 50% to 70% of patients were noted to have documented infections [2,11].

Similar trends, although less striking, have been noted in the EORTC series of studies over a 15-year span. The importance of this observation lies in the fact that patients with fever of unknown origin generally have a less complicated course following the initiation of empiric antibiotic therapy, compared with those with a documented infection on presentation. Patients with fever of unknown origin can more frequently be sustained through neutropenia by the initial empiric regimen without changes, whereas antibiotic alterations are commonly required to contain a documented infection. In addition, mortality from febrile neutropenia is lower when no infection has been documented [6-8,15].

In summary, it appears that there is a population of cancer patients who are at relatively low risk for serious complications during febrile neutropenia. Such patients often have either no documented source of infection or have a mild, relatively easily controlled infectious process. Retrospective analyses have indicated that these patients tend to do very well, with few complications, following hospitalization and the institution of broad-spectrum, empiric IV antibiotic therapy. The ability to accurately identify low-risk patients prospectively could allow for a less intensive management approach in these patients.

**Risk Factors For Infections**

Granulocytopenia is the most readily identifiable risk factor for the development of bacterial and fungal infections, and therefore, it has been assumed that all febrile patients with granulocytopenia share a common risk for these adversities. However, it is clear that these patients do not comprise a homogeneous group.

**Depth and Duration of Neutropenia**

The work of Bodey et al demonstrated that the critical determinants of the level of risk are the depth of the white cell nadir and the overall duration of neutropenia. Having < 500 granulocytes/mm³ substantially increases the susceptibility to infection, but a granulocyte count of < 100 cells/mm³ confers the greatest infection risk. The majority of bacteremias and bacterial pneumonias occur at this low granulocyte level [1,6].

Similarly, the overall duration of neutropenia has a profound influence on the risk for, and response
to, infectious complications. Many studies have confirmed that patients with the most favorable prognosis are those in whom granulocyte counts rebound early after the onset of fever. In an early study from the EORTC, the change in granulocyte count was found to be the most striking prognostic variable in neutropenic patients, regardless of the source of fever (unknown origin or documented infection) or even the antibiotic combination used to treat it. Among febrile cancer patients with low initial granulocyte counts (500 cells/mm³ or less), 88% of those who had a subsequent rise in counts had overall improvement (ie, defervescence and resolution of all signs and symptoms of infection without modification of the initial regimen), compared with only 50% of patients whose counts declined or remained unchanged [6].

At the NCI, it was noted that neutropenic patients with fever of unknown origin whose granulocyte count returned to 500 cells/mm³ or greater within the first week after fever onset had a significantly better response to initial antimicrobial therapy than those whose neutropenia lasted more than 14 days (95% vs 32%). Patients with longer durations of neutropenia were increasingly susceptible to new or recurrent bacterial infections, and 38% of those who initially defervesced had recurrent fever when neutropenia lasted more than 2 weeks. In contrast, recurrent fever occurred in 0.6% of those with a short duration of neutropenia [16]. Recurrence or persistence of fever in patients with prolonged neutropenia was frequently a harbinger of occult fungal infection. Accordingly, increasing duration of neutropenia was associated with a dramatic increase in antibiotic and antifungal modifications to the initial empiric regimen, although overall survival was equally high in all groups. Unlike patients with fever of unknown origin, those with documented infections and prolonged neutropenia have consistently been shown to have a much worse prognosis than those in whom there is prompt recovery of granulocyte counts [2,6,11].

**Modifications of Initial Empiric Antibiotics**

At the NCI, we have also found a strong correlation between the duration of neutropenia and the number of antibiotic modifications made to the initial empiric regimen. In this regard, modifications appear to be a marker for the complexity of a patient's medical course subsequent to presentation with fever. Patients whose neutropenia resolved within 10 days had few to no modifications in their initial antibiotic therapy, whereas those with more prolonged neutropenia (> 10 days) were increasingly more likely to require changes or additions in their initial regimen. Accordingly, patients in whom granulocytopenia is anticipated to resolve within 7 to 10 days of the febrile episode may be classified as low-risk patients since they are most likely to have an uncomplicated course, even in the setting of a documented infection. We have found that relatively accurate projections of neutropenia duration can be made (ie, deciding whether neutropenia will last < 7 to 10 days vs > 10 days) as increasing experience is gained with specific chemotherapeutic agents and regimens for cancer treatment.

**Clinical Characteristics Predictive of Risk**

In recent years, Talcott et al at the Dana-Farber Cancer Institute have led a concerted effort to prospectively recognize and codify risk factors that can be discerned when patients present with fever and neutropenia and that will determine the subsequent level of morbidity in those patients [17-19]. They reviewed the presenting clinical characteristics of 261 patients admitted to the hospital with fever and neutropenia and correlated them with the subsequent occurrence of life-threatening medical complications during the course of neutropenia. Medical complications that would signify a high-risk patient were identified; these included hypotension, new cardiac arrhythmias or heart failure, significant hemorrhage, new mental status or neurologic changes, pulmonary deterioration, and the development of a serious infection (eg, typhlitis, sepsis, and invasive fungal infection).

Retrospective review of patient records revealed that patients could be grouped according to presenting characteristics that correlated with high-risk outcomes: Group 1 consisted of patients who were already hospitalized at the time of onset of fever and neutropenia, suggesting that these individuals were already in poor medical condition. Group 2 were outpatients with a "concurrent comorbidity" at the time of presentation, including (most commonly) hemodynamic instability, clinical bleeding, respiratory failure, altered mental status or new neurologic symptoms, and dehydration due to inadequate fluid intake. Group 3 included outpatients with "uncontrolled cancer" at the time of presentation, which was defined as newly treated tumors; newly relapsed, refractory, or persistent leukemia; or progressive disease (new lesions or > 25% increase in old lesions since the initiation of chemotherapy). Patients with any one of these characteristics were considered to be in a high-risk group.

A fourth group of patients, who were outpatients with fever and neutropenia but without either
comorbidity or uncontrolled cancer, were designated as low risk. Among patients in each of the three high-risk groups, 34% in group 1, 55% in group 2, and 31% in group 3 ultimately developed a serious medical complication during their subsequent hospital course, compared with < 2% of patients in group 4. Similarly, an overall 17% incidence of mortality was found among those identified as high-risk patients (groups 1 to 3), whereas no deaths occurred in the low-risk group (group 4) [17]. Interestingly, the presence of bacteremia, by itself, did not appear to portend a poor outcome in the analysis by Talcott et al. Instead, outcome was influenced primarily by the presence of one of the identified high-risk factors. There was no difference in the incidence of bacteremia among the four risk groups, but when bacteremia occurred with one of the preexisting risk factors (ie, an ongoing hospitalization or an unfavorable concomitant medical condition), there was a high frequency of complications. In addition, the investigators found that duration of neutropenia, by itself, did not forecast outcome, in contrast with data from the NCI and elsewhere. In the study by Talcott et al, two-thirds of patients with short-lived neutropenia (7 days or less) also fell into a high-risk category. Nonetheless, medical complications were less frequent, overall, in patients whose neutropenia resolved in 7 days or less in this study.

In a subsequent study, Talcott and colleagues prospectively applied their risk assessment model to 444 patients with fever and neutropenia. All outpatients were admitted for IV antibiotic therapy and, based on data collected within the first 24 hours following presentation with fever, they were categorized into one of the three high-risk groups or into the low-risk group. Preexisting inpatient status at the time of fever and neutropenia, serious concurrent comorbidity within 24 hours of admission, and uncontrolled cancer were factors that, again, correlated strongly and independently with the occurrence of subsequent complications. Overall, medical complications occurred in 34% of the 340 patients included in the three high-risk groups but in only 5% of the 104 low-risk patients. All complications among low-risk patients were either asymptomatic or transient, and all were readily detected by routine follow-up, before more serious consequences occurred [18].

**Outpatient IV Antibiotics**

Outpatient IV antibiotic therapy has gained wide acceptance for the completion of prolonged courses of antibiotics in patients who have rather chronic infections but are not acutely ill. Endocarditis and osteomyelitis are disorders for which this approach has proved to be a reasonable, less costly alternative to inpatient therapy. The development of programmable, portable infusion pumps to deliver multiple, timed IV infusions has permitted the application of this approach to the outpatient setting. Whether it is IV or oral, outpatient therapy is most appropriate for patients who are anticipated to be medically stable over time [20]. For the febrile neutropenic cancer population, those selected by low-risk criteria should be the best candidates for outpatient therapy.

**Multiple-Dose IV Antibiotics**

Using a modified version of their assessment model for prospectively determining the level of risk among febrile neutropenic cancer patients (outlined above), Talcott et al piloted the use of home IV antibiotic therapy in low-risk cancer patients with fever and neutropenia [19]. In addition to exclusions based on one of the three predesignated high-risk categories, patients were also categorically excluded if they had a significant documented infection, such as bacteremia, urinary tract infection, and pneumonia, or if they were 65 years of age or older. These additional criteria were incorporated into the protocol to further reduce risk. Patients were hospitalized and IV antibiotics (either mezlocillin [Mezin] plus gentamicin or ceftazidime alone) were initiated. Following a 36- to 60-hour in-hospital observation period, 30 low-risk patients were enrolled and discharged home to receive the remainder of their antibiotic course via programmable pumps. Premixed medications were delivered to the home every few days, and a health-care professional made daily visits. Patients were initially required to have a companion who could care for them at home around the clock, and they had to be within a 1-hour drive of the hospital, although these restrictions were relaxed as the study progressed. The mean duration of neutropenia among the 30 home-therapy recipients was 6 days, although 5 patients had 13 to 36 days of neutropenia. Five patients had mild clinically documented infections (cellulitis in four patients and a possible dental abscess in one individual). Patients were treated with IV antibiotics at home for a median of 3.5 days (range, 1 to 24 days). However, 9 (30%) of the 30 home-treated patients required readmission to the hospital. Four of these had medical complications and five others required antibiotic additions to treat recurrent or prolonged fever. In five additional patients, modifications had to be made to the initial antibiotic therapy after discharge.
Complications of home therapy included hypotensive episodes, acute renal failure, prolonged fever, and the development of new documented infections during treatment (eg, mucormycosis, *Staphylococcus epidermidis* sepsis, cellulitis). Although none of these complications resulted in death or permanent disability, they occurred in 13% of study participants, compared with the 5% rate of complications in low-risk patients defined by similar criteria in prior trials. It is notable that three of the four complications occurred in patients with > 7 days duration of neutropenia, as did most of the antibiotic additions for prolonged fever or new infections.

The high rates of hospital readmission (30%) and modifications to the initial empiric antibiotic regimen (approximately 50%) that occurred among low-risk patients enrolled in this pilot study have raised questions about the practical utility of the Talcott prediction criteria [21]. It is possible that the inclusion of patients with relatively prolonged durations of neutropenia, particularly those with leukemia, produced these unfavorable results.

Not unexpectedly, patients treated at home generally described an increased sense of well-being. In addition, there was a significant reduction in daily medical costs associated with home therapy, as compared with inpatient treatment in a group of similar patients. Nonetheless, outpatient IV therapy appeared to be a cumbersome approach. Nearly half of the medically eligible patients declined to enter the study because they were anticipated to have only a few days of neutropenia. Presumably, these patients felt that it was more convenient to be cared for in the hospital, without the imposed responsibilities of antibiotic delivery, storage, and self-administration at home.

At the University of Texas M.D. Anderson Cancer Center, more encouraging results have been reported with the outpatient administration of aztreonam (Azactam) plus clindamycin for neutropenic fever [22]. Low-risk patients were selected by criteria similar to those of Talcott et al, but the overall response rate was 95% in the 43 patients receiving outpatient IV antibiotics, and no patient required hospital admission, in contrast to the less favorable results of the former study. Fewer patients with leukemia or prolonged neutropenia were included in this study, compared with that performed at Dana-Farber, and this may account for the improved outcome observed.

**Ceftriaxone Plus Once-Daily Aminoglycoside**

Several groups have evaluated simplified IV regimens composed of ceftriaxone (Rocephin) plus a once-daily aminoglycoside dose, which can be readily exported to the outpatient setting [8,10,23]. Ceftriaxone has a broad spectrum and a particularly long half-life, allowing for convenient once- or twice-daily administration to achieve bactericidal serum levels. Although ceftriaxone is nearly identical in spectrum to ceftazidime, the former agent lacks adequate activity against *P aeruginosa*. However, in an era in which *P aeruginosa* is a less frequent pathogen in neutropenic patients, ceftriaxone may be an adequate alternative, especially in low-risk populations. Once-daily administration of aminoglycosides yields high peak serum concentrations that provide maximal bacterial killing. This schedule also appears to be less nephrotoxic and ototoxic than traditional repetitive aminoglycoside dosing.

In a nonrandomized, uncontrolled pilot study, Martino et al administered once-daily ceftriaxone plus amikacin to 46 neutropenic patients with fever and underlying leukemias or lymphomas, who had a relatively long mean duration of neutropenia of almost 2 weeks [23]. No low-risk selection criteria were applied to this patient population, although all of them were outpatients at the time that they developed fever, in accordance with one of the major criteria of Talcott et al. Their outpatient status may have been a marker for an absence of significant comorbidity. Nonetheless, four patients who ultimately responded to therapy presented in septic shock. After therapy was initiated, patients were observed in a short-term ward for an unspecified period and were discharged when they were afebrile and had no clinical signs of infection.

Although the details of study entry and execution are sparse, the results suggested that outpatient antibiotic therapy was a feasible option in some patients. Antibiotic courses for febrile neutropenia were successfully completed, either at home or at daily clinic visits, in 37 of 49 febrile episodes without modification (76% response rate).

Two large randomized trials have compared the once-daily regimen of ceftriaxone plus an aminoglycoside with multidose combination regimens for inpatient therapy of febrile neutropenia. No differences in outcome were detected between patients in the two treatment groups in these studies, and the few patients with *P aeruginosa* infections fared well when appropriate antibiotic modifications were made [8,10].

The accumulated data indicate that a daily regimen of ceftriaxone plus an aminoglycoside should be adaptable to the outpatient venue, provided that the incidence of *P aeruginosa* and other resistant organisms is low in a given patient population. Since the schedule of once-daily IV administration is considerably simpler than multiple dosing schemes for outpatient therapy, it may be more
acceptable to both patients and caregivers. A randomized trial of inpatient vs outpatient IV antibiotic therapy has yet to be performed, however, so it is not possible to endorse wide use of outpatient IV antibiotics for patients initially presenting with febrile neutropenia. Nevertheless, in the context of existing data, selected patients who have rising granulocyte counts, an anticipated brief duration of neutropenia, and improving signs of infection or the absence of infection may be appropriate candidates for early discharge and completion of their antibiotic course in the outpatient setting, as long as vigilant follow-up is ensured.

**Outpatient Oral Antibiotic Therapy**

The simplest approach to the management of low-risk patients with fever and neutropenia is to use potent broad-spectrum oral antibiotics in an outpatient setting. This strategy precludes the requirements for hospitalization or for outpatient administration of IV agents, with the attendant complexities of premixing, delivering, and storing IV antibiotics. The oral fluoroquinolones have a broad antibacterial spectrum and excellent oral bioavailability, making them excellent candidates for outpatient oral therapy. Given orally, such agents as ciprofloxacin (Cipro), pefloxacin, and ofloxacin (Floxin) achieve bactericidal serum drug levels against most of the gram-negative pathogens that afflict the neutropenic host. However, the activity of ciprofloxacin against gram-positive species, particularly streptococci, is less reliable. Therefore, ciprofloxacin should be used in combination with a second agent, such as a beta-lactam drug or macrolide, that provides better gram-positive coverage. Ofloxacin, on the other hand, has less efficacy against *P. aeruginosa*, although it has excellent activity against most of the gram-positive and many of the enteric gram-negative pathogenic bacteria. If the incidence of *P. aeruginosa* infections in a given cancer population is very low, ofloxacin may provide sufficient empiric coverage.

**Studies of Ofloxacin**

A series of studies investigating oral ofloxacin for the treatment of cancer patients with fever and neutropenia have been performed by Malik et al in Pakistan [24-26]. These investigators were prompted to explore oral therapy due to the substantial costs associated with inpatient management of neutropenic fever-an expense that cannot be borne by many patients in an economically disadvantaged country. In an initial small randomized study, they found equivalent rates of response to oral ofloxacin and a parenteral beta-lactam-aminoglycoside combination among hospitalized cancer patients with febrile neutropenia [24]. Excluded from study were patients with concomitant medical conditions that were felt to confer increased risk, such as renal or hepatic dysfunction, signs of sepsis, and inability to take or absorb oral medication (eg, due to painful oral mucositis, nausea and vomiting, or intestinal malabsorption), but there were no restrictions on the anticipated duration of neutropenia.

Overall, success, with and without modifications of the initial regimen, was 77% for oral ofloxacin therapy vs 73% for parenteral antibiotic therapy. Mortality was 7% with ofloxacin and 10% with combination therapy. As predicted by earlier studies, patients with fever of unknown origin fared substantially better than those with documented infection, regardless of the initial antibiotic regimen (88% vs 65% response rates). Furthermore, there was a striking correlation between neutropenias lasting < 1 week and successful outcome, again demonstrating that the duration of neutropenia is a major determinant of risk status. Based on these findings, the authors redefined their high-risk criteria to include patients in whom there was an expectation of prolonged neutropenia (ie, 7 days or greater).

In two subsequent trials involving nearly 300 patients, Malik et al again demonstrated that over 75% of the low-risk febrile neutropenic episodes could be successfully treated with oral ofloxacin, without any requirement for modifications to this initial empiric coverage. The majority (195) of these patients were treated outside of the hospital environment, and often a long distance away, with medical follow-up often limited to telephone communication and every-other-day clinic visits. Hospital readmission, due to failure of oral ofloxacin therapy (defined as fever persisting for > 4 days), occurred in approximately 18% of the 195 outpatients evaluated, and most of these patients responded to the institution of parenteral antibiotics. Many of the patients who required readmission had an unexpectedly prolonged duration of neutropenia, lasting 1 week or greater. Overall success, with or without modifications to initial therapy, was 97% for outpatients treated with oral ofloxacin, which is comparable to success rates for inpatient therapy with oral or IV antibiotics.

This high rate of success appears to validate the low-risk criteria employed by these investigators, namely, the absence of a significant medical comorbidity and the anticipation of a brief neutropenic
period. It is of concern, however, that several outpatients may have died because they developed nausea and vomiting, resulting in poor antibiotic absorption, or because they could not comply with protocol requirements. The authors emphasize the need for maintaining "strict vigilance, close patient-physician contact, and a high degree of patient compliance in order to achieve a successful outcome" for outpatients who are treated orally for fever and neutropenia [25,26].

**Studies of Ciprofloxacin Combinations**

In the United States, investigators at the University of Texas M.D. Anderson Cancer Center have explored the oral combination of ciprofloxacin and clindamycin for low-risk patients with fever and chemotherapy-induced neutropenia [22]. They identified low-risk patients primarily by excluding individuals with certain significant comorbid medical conditions or symptoms. Patients with documented infections, those who were expected to have long neutropenia, and those over age 65 were eligible for study. All patients in the low-risk category were randomized to receive either an IV regimen (aztreonam plus clindamycin) or the oral combination regimen, each provided strictly in the outpatient setting, following initial dosing during a brief observation period in the clinic (ie, 2 to 8 hours).

High rates of success were reported for patients with fever of unknown origin who were treated orally (91%), as well as for those with documented infections (81%). However, 6 (15%) of 40 patients receiving oral therapy required hospital admission for failure to respond or the development of renal toxicity. In contrast, none of the 43 patients treated with the outpatient IV combination required hospital admission or developed renal toxicity. The high rate of complications occurring on the oral regimen suggested that oral ciprofloxacin plus clindamycin was not as safe or effective as the IV regimen of aztreonam plus clindamycin.

In a second study, the M.D. Anderson group changed their oral regimen to ciprofloxacin plus amoxicillin/potassium clavulanate (Augmentin), which again yielded a high response rate of 88% for low-risk outpatients, with no deaths, complications, or toxicities [27]. It is notable that a high proportion of patients with microbiologically or clinically proven infections were included in these studies, suggesting that the careful selection of patients, as well as attentive medical care, may permit the outpatient management of documented infections even in the setting of neutropenia. At the NCI, we are currently enrolling inpatients in a randomized, double-blind comparison of oral ciprofloxacin plus amoxicillin/clavulanate vs IV cef-tazidime, to determine whether these treatment regimens are equally efficacious in managing low-risk patients. Our low-risk criteria include patients with an expected duration of neutropenia of < 10 days and no evidence of severe medical comorbidity, such as pneumonia, hypotension, gastrointestinal dysfunction, neurologic changes, severe mucositis, nausea and vomiting, and other factors that could interfere with oral intake and absorption. Although this study remains blinded, it can be assumed that half of the 150 low-risk febrile neutropenic patients enrolled thus far have received oral antibiotics, without any major complications or deaths.

**General Guidelines**

Oral therapy should be considered only for those patients who are able to swallow pills and who have no gastrointestinal dysfunction. Patients must not take antacids concurrently with fluoroquinolones, since divalent cations, such as Ca++, Mg++, and Al++, will chelate these drugs and prevent their absorption. It is especially important to avoid fluoroquinolone therapy in any patient who develops fever or a documented infection while receiving fluoroquinolone prophylaxis, due to the concern that breakthrough fevers during fluoroquinolone prophylaxis may be due to fluoroquinolone-resistant pathogens.

**Early Hospital Discharge**

Once empiric antibiotic therapy has been initiated for fever and neutropenia, patients have traditionally remained "covered" at least until their granulocytes return to the level of 500 cells/mm³ or more. At the NCI, early discontinuation of antibiotics, prior to recovery of the neutrophil count to > 500 cells/mm³ was found to be associated with a high incidence of recurrent fever due to recrudescence of the original infection or to occurrence of a new bacterial or fungal infection [28]. However, most of the patients studied had extended periods of neutropenia after stopping antibiotics.

Recent evidence from a series of pediatric studies performed by the group at University of Texas Southwestern suggests that antibiotics might be discontinued safely prior to the attainment of 500 granulocytes/mm³ in a defined subset of low-risk patients [29]. In a prospective study of 131 episodes of fever and neutropenia secondary to cancer chemotherapy, patients (all pediatric) were
initially hospitalized for broad-spectrum IV antibiotics but were eligible for discontinuation of IV agents and discharge home when they met the following criteria: afebrile for 24 hours, appeared clinically well, negative cultures for a least 48 hours, local control of any infectious process, and evidence of bone marrow recovery for at least 1 day (as measured by rising absolute neutrophil, total leukocyte, or platelet count) [30]. Intravenous antibiotics were discontinued despite an absolute neutrophil count of < 500 cells/mm³ in 82 patient-episodes. In nearly one-third of these, the patient was switched to oral antibiotics to complete therapy for resolving infections, including bacteremia, pneumonia, sinusitis, and otitis. Seventy-eight children were discharged early, but it was retrospectively discovered that eight of them had been inadvertently discharged without evidence of marrow recovery. Of these eight children, six required readmission to the hospital for complications. In contrast, only 1 of the 70 children who met all low-risk criteria for early discharge had to be readmitted for recurrent fever. Estimated mean savings in hospital costs were over $5,000 per patient for those discharged early.

Early discharge, without antibiotic coverage, may be an option for a very select subset of low-risk patients, as long as they have specific evidence of impending bone marrow recovery. Jones et al studied the effect of early discontinuation of antibiotics in neutropenic patients who were treated for fever alone, with no discernible sites of infection and negative cultures (ie, those with fever of unknown origin), and prompt defervescence. These researchers demonstrated that the risk for recurrent fever after stopping antibiotics was low in patients with "good potential of marrow recovery"[31]. However, fever occurred in 45% of patients with fever of unknown origin who discontinued antibiotics during persistent granulocytopenia without signs of improving marrow function.

More studies are necessary to affirm that early discontinuation of antibiotics is as safe and effective as a "full course" of therapy through the period of neutropenia. Although it is clear that marrow recovery is the most critical feature of this algorithm, it will be important to designate very specific laboratory criteria that can accurately predict imminent marrow recovery in the majority of cancer patients, in order to guide oncologists in this endeavor. Stopping antibiotic therapy too early can lead to dramatic clinical deterioration in patients who remain granulocytopenic, especially if they are persistently febrile or have an occult infectious process.

Impact of CSFs and Stem Cells on Risk

With the development of the colony-stimulating factors (CSFs), granulocyte CSF (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage CSF (GM-CSF, sargramostim [Leukine]), and the application of peripheral stem-cell rescue techniques, we must carefully consider the implications of these adjunctive therapies on risk assessments and the possible use of outpatient antibiotic therapies. In many circumstances, these therapies can significantly shorten the neutropenic duration expected from a given chemotherapeutic regimen. Exerting a profound influence on this important risk factor-ie, the duration of neutropenia, or (more accurately) the rate at which the granulocyte count returns-CSFs and stem-cell infusions can potentially convert a high-risk situation to one that is, perhaps, a lower-risk process. However, interventions that promote more rapid return of the granulocyte count are often used to allow for higher dose intensity of chemotherapy regimens. Consequently, although the duration of neutropenia may be shortened by the use of CSFs or stem-cell reinfusions, there may be more mucositis, dehydration, renal or liver toxicity, or immunologic suppression associated with the dose-intensive cancer chemotherapy. These comorbidities may confer increased risk to patients, even in the setting of brief neutropenia. In an ongoing study at the NCI, the infusion of G-CSF-mobilized, peripheral blood progenitor cells following marrow-ablative chemotherapy has resulted in a mean neutropenia duration of only 7 days, but the incidence of documented infection is close to 50% in 43 cycles completed thus far. Bacteremia has complicated 23% of those cycles. Severe gastrointestinal mucositis appears to be related to the high frequency of documented infections in this patient group (L. Wexler, personal communication, March 1996).

This problem illustrates the point that although we can manipulate the duration of neutropenia, we must be aware of the emergence and importance of other factors associated with intensive chemotherapy that contribute significantly to a patient's overall risk for complications.

Conclusions

In a practical sense, it is clear that the trend toward simplified medical approaches to febrile neutropenic patients is economically imperative. The powerful financial forces that are currently
shaping health care have compelled us to seek less expensive, yet still effective strategies for all forms of medical management, including the supportive care of cancer patients. The economic advantages of the outpatient approach to febrile neutropenia are abundantly clear. Improvement in the quality of life for cancer patients is intuitively apparent. However, fever with neutropenia in a cancer patient is a potentially life-threatening condition, and outpatient therapies have heretofore addressed only the most stable of patients who require relatively short antibiotic courses. With the studies described herein, medical management of potentially serious conditions has achieved a new level of divergence from standard care (Table 3). The discharge and treatment of neutropenic patients with either documented or occult infections (which may present as fever of unknown origin), even if they fit low-risk criteria, require more rigorous study before such an approach can be widely accepted.

It is important to recognize that low-risk criteria are generalizations based on population studies, and they cannot necessarily be applied blindly to each individual patient to fully predict that patient's course. Talcott et al state that "no model can foresee all circumstances.... A patient who is at low risk is not at no risk...." [19]. Febrile neutropenic patients, including those classified as low risk, are prone to rapid and serious alterations in their medical condition. Accordingly, the selection and follow-up of low-risk patients must involve good clinical judgment. Regardless of the type of empiric antibiotic therapy or the setting in which it is given, it is critical that initial therapy be followed by frequent patient assessments, with modifications made in response to clinical and microbiologic data that emerge during the course of neutropenia. Outpatients, in particular, should be observed closely, with a low threshold for modifying treatments or for hospital admission, as clinical circumstances change.

Logistical Questions to Be Addressed

The successful application of outpatient antibiotic therapy for febrile neutropenia requires the development of standards of outpatient care for patients with a potentially life-threatening condition. This includes specific plans to implement careful, open communication between physicians and patients, vigilant medical follow-up, and ready access to intensive in-hospital interventions should a problem arise during outpatient treatment. A number of logistical questions must be addressed:

What, precisely, are the most reliably predictive low-risk factors?
How long should a patient be observed in the clinic or inpatient setting before outpatient therapy is employed: several hours or several days?
How far from a hospital can the patient reside, and what type of companion care should be available?
How frequently should a patient be seen for vital signs and physical examinations, either at home or in the clinic, and how often should he or she have blood tests or x-rays?
What specific events or symptoms should prompt a return to the hospital for examinations, tests, or, especially, readmission?

The studies reviewed above show that outpatient antibiotic therapy is undoubtedly feasible and probably safe for a select group of low-risk patients who present with fever and neutropenia. However, until there is a larger body of knowledge available to answer many of these questions and develop reasonable guidelines for outpatient therapy, this approach cannot yet be considered a routine alternative to inpatient treatment of febrile neutropenia. Therefore, it is imperative that we continue to acquire experience with managing cancer patients at home or in the clinic, via clinical trials performed in the context of our changing health-care delivery systems. Hopefully, with this experience, we can safely offer patients the benefits of increased time at home during the treatment of cancer.

References:
6. EORTC: Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients.

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