The discussion by Freifeld and Pizzo is a comprehensive summary of an important recent trend: the attempt to identify low-risk patients with fever and neutropenia and relax their therapy appropriately. It is not surprising that a summary from these authors would be definitive. Dr. Pizzo and his colleagues have defined many central elements of the therapy of fever and neutropenia: that broad-spectrum antibiotics should be continued after patients become afebrile while they remain neutropenic [1]; that an antifungal agent, amphotericin, should be added to prevent potentially serious fungal superinfection when patients remain febrile and neutropenic after 7 days [2]; and that monotherapy using ceftazidime alone is as effective as combination therapy with a semisynthetic penicillin and an aminoglycoside, particularly for low-risk patients [3]. Their current review catalogs recent attempts to define less aggressive, costly, and restrictive therapy for low-risk patients with fever and neutropenia. I would add only a few comments based on our work at the Dana-Farber Cancer Institute.

My belief that there exist low-risk patients with fever and neutropenia appropriate for less aggressive therapy stems from: (1) the clinical impression that some patients have predictably benign courses and (2) the hypothesis that "uncomplicated" fever and neutropenia is a self-limited condition, assuming that the patient is appropriately supported with broad-spectrum antibiotics, since adequate production of granulocytes and re-establishment of the gastrointestinal integument soon restore the patient's usual barriers to infection. Unless interrupted by additional problems, such as an unusually serious infection, a structural problem with the gut mucosa (eg, a locally invasive tumor), or a myelophthisic tumor interfering with production of bone marrow elements, patient recovery proceeds smoothly and promptly.

Of course, patients receiving cytotoxic chemotherapy for cancer have, by definition, other medical problems besides the effects of cytotoxic chemotherapy. If nothing else, they have the cancer that the chemotherapy was initiated to combat, the cumulative effects of prior therapy, or other comorbid illnesses common in the older age groups in which cancer is most common. Therefore, the goal of risk assessment, as I see it, is to use clinical information to distinguish uncomplicated patients with febrile neutropenia from those with additional problems that place them at higher risk of medical complications.

Is Expected Duration of Neutropenia an Independent Predictor of Risk?

Our goal was to assess risk in febrile neutropenic patients as early as possible after presentation using clinical characteristics available to the treating clinician, in order to help guide management decisions. Therefore, we evaluated only risk factors that could be determined within 24 hours of presentation [4,5]. While the work of Pizzo and colleagues [6] and of Bodey and colleagues [7] has consistently affirmed the prognostic impact of longer vs shorter periods of neutropenia, the duration...
of neutropenia can be determined with certainty only when the episode of febrile neutropenia is over, when management decisions have already been made. Whether the predicted duration of neutropenia is also an independent predictor of patient risk is an empirically answerable question: Simply add the pretreatment prediction of neutropenia duration to variables assessed and enter it into a multiple regression model. When they identified brief neutropenia as a marker of good risk, Pizzo and colleagues reported that they were unable to find clinical predictors of it [6], although Freifeld and Pizzo now state that they can predict duration of neutropenia more accurately. However, when we retrospectively applied the actual duration of neutropenia to our patient population, we found that patients with neutropenia of < 7 days indeed had a lower risk, but their overall risk of major medical complications was 16%, as compared with 5% for the patients in our own low-risk group [5].

Medical Risk: The Fundamental Issue in Outpatient Therapy
Freifeld and Pizzo correctly point out that, absent a randomized trial showing equivalence between standard IV antibiotic regimens given in the hospital and the same regimen given at home, outpatient therapy per se has not been assessed and thus cannot be considered the standard of care. Other approaches to simplifying care, including the use of oral regimens, simplified intravenous (IV) regimens, and early discontinuation of antibiotics, may ultimately contribute elements to a safe, easy-to-administer outpatient regimen, but now represent additional experimental variables, in addition to the site at which care is delivered. The primary characteristic of home care, as compared with standard in-hospital care, is the necessarily lower level of surveillance possible for patients at home. Therefore, if patients are at too high a risk of serious medical problems requiring immediate intervention, treating them at home would be unwise and potentially harmful. To alter both the site of care and some other element of care, such as the route of antibiotic administration, changes two variables in a single trial, making the effect of treatment at home per se on any outcome difference difficult to identify. The outcome used to compare efficacy is also important. Death is unarguably important but is too uncommon among low-risk patients for a trial with death as the primary end point to have both adequate power and manageably low patient numbers. The problem that death is important but uncommon has led to the troubling finding in some trials of an extra death in the outpatient group—a statistically insignificant outcome that, nevertheless, substantially undermines the conclusion that the two approaches are equally safe and efficacious [8,9]. In our ongoing Cancer and Leukemia Group B randomized trial of in-hospital IV antibiotic therapy vs early discharge to home IV antibiotic care for low-risk patients, we use the occurrence of major medical complications, defined as serious problems for which an emergent intervention is necessary, as the primary end point. While this is a more ambiguous outcome than death, it is more common and is, we believe, logically linked to the issue of medical risk, the fundamental issue in home therapy of febrile neutropenia. These technical points aside, Freifeld and Pizzo have done an excellent job of summarizing the changing approach to identifying and treating low-risk patients with fever and neutropenia.

References:

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