Multicentre Canadian clinical trials on neutropenic patients

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NEUTROPENIA (USUALLY DEFINED AS LESS THAN 500 neutrophils per microlitre) is occurring more frequently because of the increasing use of aggressive approaches for the tr atment of malignant disease as well as new indications for immunosuppressive chemotherapeutic agents such as cyclophosphamide. The majority of neutropenic patients are patients with solid tumours, hematological malignancies (acute and chronic leukemias and lymphomas) and those undergoing bone marrow transplantation (autologous or allogeneic); the latter are primarily patients with malignant disease.

Neutropenia predisposes to infectious complications and makes it difficult for patients to respond to appropriate antimicrobial therapy. A number of factors associated with neutropenia influence outcomes in patients treated for fever associated with their neutropenia, including degree of neutropenia, duration of neutropenia, underlying malignancy, state of the underlying malignancy, organism cultured (if any) and site of infection. The relationship of these factors to outcome will be addressed briefly.

Patients with severe neutropenia (less than 100/μL) have a much greater chance of developing infection and are much less likely to respond to appropriate antimicrobials. This must be considered when designing clinical trials and when interpreting publications dealing with such trials.

The duration of neutropenia is also very important. Patients whose neutrophil count drops to below 500/μL for a few days and even up to a week, usually have a very good outcome regardless of the empiric antibiotic therapy used to treat the febrile episode. Beyond seven days, there is an intermediate risk for developing infection and an intermediate response to therapy, and beyond 14 days there is a significant risk. At special risk are patients who remain severely neutropenic (less than 100/μL) for longer than two weeks. These patients often make up only a small part of many of the published studies unless the major patient population being studied are patients with acute leukemia (especially acute myelogenous leukemia) or patients undergoing bone marrow transplantation. This must also be considered when designing and interpreting trials.

The type of underlying malignancy also seems to be important. Patients who have acute leukemia or undergo bone marrow transplantation seem to be at the highest risk of developing infection and having difficulty with appropriate intervention. Although part of this can be explained on the basis of the degree of neutropenia associated with their chemotherapeutic regimens, this does not seem to be the entire explanation. The aggressively treated hematological malignancies seem to be more prone to infectious complications. Because of the nature of the chemotherapeutic regimens, patients with hematological malignancies also have long duration neutropenia. Perhaps the chemotherapy creates serious mucositis which in many cases is part of the problem. This is less common with chemotherapy of solid tumours.

Whether the patient is in remission or relapse also seems to be important. The patients who are in remission, even if they become neutropenic associated with consolidation therapy, have less frequent infections and a much better chance of recovering from the infection. This is even true in patients who eventually go into remission during induction therapy of acute myelogenous leukemia compared to those who do not respond to the first therapy. Many of the infectious complications respond much better in patients in remission. In addition, unusual infections may occur,

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eg, infections with multiresistant organisms or unusual organisms such as fungi, often occur in patients who have had multiple relapses. This may relate to, eg, the state of the disease or to the previous use of antimicrobials.

Specific organisms may cause infection in patients with febrile neutropenic episodes. In the 1960s and 1970s, Gram-negative bacilli including enterobacteriaceae (especially *Escherichia coli*, klebsiella and serratia) and *Pseudomonas aeruginosa* were the most frequent etiological pathogens. In recent years, Gram-positive pathogens especially *Staphylococcus epidermidis* and *Staphylococcus aureus* have become much more frequent and usually they are more frequently isolated than Gram-negative pathogens. The appearance of Gram-positive infections is almost certainly due in part to the increased use of central lines such as Hickman catheters and Portocaths. In addition, some groups argue that colonization of the gastrointestinal tract by Gram-positive pathogens, particularly *Staph epidermidis* may then invade and cause infections in such patients, especially when severe mucositis occurs throughout the gastrointestinal tract. Other Gram-positive pathogens such as *Streptococcus viridans* and enterococcus have become more common in recent years and emphasize the changing pattern of organisms in neutropenic patients.

Similar patterns of changing pathogens are seen around the world, at least in developed countries. Individual hospitals, countries, etc, must continuously be aware of the organisms causing infections in their institutions, since this should influence the approach to empiric antimicrobial therapy. Therefore, some of the recommendations based on the results of studies that are done today may have to be changed in the future because of changing pathogens.

The most difficult infections to deal with in neutropenic patients are pneumonias and bacteremias. Urinary tract, gastrointestinal and soft tissue infections, although troublesome, are certainly less difficult to treat. An imbalance of these infections on two arms of a randomized trial might influence the outcome. A significant number of patients will have pneumonias and soft tissue infections as the source of infection but in which no organism is found (**documented infections**). Documented infections seem to do as badly as those in which organisms are actually identified. There is also a group of patients who have febrile episodes for which no site or organism is found. These have been referred to in the past as fevers of unknown origin, but more recently have been called **unexplained fevers**. The latter behave similarly to documented infections in that untreated patients may go on to suffer serious problems, but probably have a slightly better prognosis than patients with documented infections. In many series, the unexplained fevers make up between 40 and 60% of cases.

PROPHYLAXIS

Another important factor that is difficult to discuss in detail is whether antimicrobial prophylaxis is appropriate and if so which antimicrobial agents to use. There is debate worldwide whether it is necessary to use oral antimicrobial prophylaxis since it is difficult to show differences in mortality in treated versus untreated populations. Also, the number of febrile episodes is often the same whether prophylaxis is used. The difference is in the number of proven infections. Another argument is that if prophylactic agents are used then one will select out multiresistant organisms or it will preclude the use of the prophylactic agents as therapy for possible febrile episodes. This latter issue is particularly important in the case of the quinolones which might be used after an initial response to parenteral therapy or even as part of initial therapy when parenteral quinolone agents are marketed. The two major choices for antimicrobial prophylaxis, when used, are cotrimoxizole and oral quinolones. When either of these agents are used, the number of documented Gram-negative infections decreases and, when oral quinolones are used, the number of Gram-negative bacteremias is reduced to almost zero. However, as previously mentioned, the number of febrile episodes remains the same and when pathogens are isolated they are frequently Gram-positive. This, therefore, may influence therapy when the patient becomes febrile.

More recent studies on prophylaxis have tried to add Gram-positive coverage (such as penicillin, erythromycin or rifampin) to quinolones to see if the number of Gram-positive infections can be reduced along with the number of febrile episodes. Even the use of prophylactic intravenous vancomycin has been advocated by some groups in the United States to reduce the frequency of Gram-positive infections. Therefore, whether prophylaxis is used and what type may influence the outcome of studies testing specific empiric antibiotic regimens. This data should be included in any study report.

EMPIRIC THERAPY

It has been known since the 1970s that empiric antibiotic therapy is indicated in patients who develop significant fevers while neutropenic, unless it can be explained by other causes such as transfusions. A variety of approaches have been used with the most frequent and accepted approach worldwide being an aminoglycoside plus an antipseudomonal penicillin. Other options include double beta-lactam combinations such as a third generation cephalosporin along with an antipseudomonal penicillin. The latter gives excellent results compared to aminoglycoside combinations but may result in multiresistant organisms associated with beta-lactamases. Monotherapy has been used successfully with third generation cephalosporins such as ceftazadime and cefoperazone, as has treatment with carbopenems such as imipenem-cilastatin.

TABLE 1
Unanswered questions

Empiric therapy of febrile neutropenic patients

Is monotherapy appropriate? What agents should be used?
Is empiric vancomycin necessary?
How long should antibiotics be continued?
What empiric antifungal should be used? When? For how long?
What method(s) of response evaluation should be used (Pizzo's *, EORTC, IHS)
What antibiotics (antifungals) should be used for modification and in wht order?
What are the prognostic factors which help identify high risk versus low risk patients?

Empiric therapy or therapy of proven fungal infections

Amphotericin B versus amphotericin B-liposome preparations
Amphotericin B versus fluconazole or saperconazole
How long to continue antifungal therapy
Value of CSF preparations in this situation

Prophylaxis

Antibiotics

Any (placebo)
Cotrimoxazole, quinolones or quinolones plus Gram-positive coverage?
What Gram-positive coverage?
Should they be continued during antibiotic therapy?

Antifungals

Any (placebo)
Ketoconazole
Fluconazole
Saperconazole
Dose and duration

Antivirals

Any
Acyclovir
Gancyclovir

Biological response modifiers

Can antimicrobial prophylaxis give the same results as CSF preparations, especially in patients with solid tumours?
Use of monoclonal antibodies to endotoxin in this population?

*CSF Colony stimulating factor; EORTC European Organization for Research on Treatment of Cancer; IHS Immunocompromised Host Society; *Pizzo PA, Hawthorn JW, Hiementz J, et al. A randomized trial comparing ceftazadine alone with combination antibiotic therapy in cancer patients with fever and neutropenia.* N Engl J Med *1986;315:552-8*

Combination antibiotic therapy is still commonly used throughout the world despite the recent presentation of data comparing ceftazadime alone to tobramycin plus piperacillin in more than 1000 severely neutropenic patients. However, in the near future, there will probably be increased use of ceftazadime alone. Imipenem-cilastatin seems to be at least as effective as ceftazidime, especially when used in high doses (4 g/day). It also seems to have a high propensity for nausea and possibly an increased likelihood of seizures. Using lower doses of imipenem-cilastatin, seems to be as effective, but no direct comparison of two doses of imipenem has yet been carried out to assure equal efficacy in this setting. A new carbapenem (merepenem) may prove to be at least as efficacious as imipenem-cilastatin with less toxicity.

Often, patients fail to respond (become afebrile) until their neutrophil count recovers significantly. In this setting, modifications with additional antibiotics are often necessary. Frequently, vancomycin is added when Gram-positive infections are proven. Based on recent studies, there is no obvious need to use empiric vancomycin as part of initial therapy, but it can be added when a proven Gram-positive infection is documented, or in some cases when a patient is clearly not responding. It is also usual to add empiric intravenous amphotericin B between day 4 and day 10, usually about day 7, if patients are not responding either to initial or modified empiric antibiotic therapy. There is some evidence that this is beneficial, especially in patients who remain severely neutropenic for prolonged periods of time.

Antifungal prophylaxis with nystatin or ketoconazole are not clearly established as beneficial. There are too few data to evaluate the benefits of the newer triazoles such as fluconazole. The use of trizoles is not established either as prophylaxis or after failed antibiotic therapy, but studies are ongoing. There is currently no evidence for prophylactic or therapeutic antiviral therapy. Perhaps the exception is in the bone marrow transplant population where *Herpes simplex* virus is often associated with mucositis in the mouth and will respond to either prophylactic or therapeutic acyclovir.

The duration of empiric antibiotic therapy is controversial with a high proportion of investigators recommending continuing antimicrobial therapy until the neutrophil count recovers to greater than 500/μL; however, some investigators recommend discontinuing antibiotics – to avoid continued toxicities and resistance – after the patient has been afebrile for approximately five days, even if the neutrophil count has not recovered.

ANSWERED QUESTIONS

Many of the answered questions have been eluded to in the previous sections. These include the fact that one should use empiric antimicrobial therapy, either an aminoglycoside combination or monotherapy with agents such as ceftazadime or imipenem-cilastatin. Modifications will often be required with agents such as vancomycin or the addition of an aminoglycoside in some cases where monotherapy is unsuccessful. Vancomycin is probably not indicated as initial therapy. Most people feel that the addition of intravenous amphotericin B is a required part of empiric therapy when patients do not respond. Prophylaxis is clearly controversial, but it results in fewer Gram-negative bacteremias especially when quinolones are used.

UNANSWERED QUESTIONS

Unanswered questions can be divided into those relating to empiric antibiotic therapy for febrile neutropenic episodes; those dealing with empiric or definitive

therapy of proven fungal infections; prophylaxis with antibiotics, antifungals and antivirals; and biological response modifiers (Table 1). All these possibilities were discussed during the workshop and a number of trials were recommended for possible further study.

What premedication is necessary when using amphotericin B for the therapy of febrile neutropenic patients? The possibilities include no treatment to a multiplicity of agents including antihistamines and analgesics. It was felt that as amphotericin B was used frequently in neutropenic patients, the number of patients required for a randomized study should be easy to accrue. The difficulty might be to decide on what is to be compared, that is nothing versus the most aggressive treatment or something in between. This trial should be pursued further either through the Canadian Infectious Disease Society (CIDS) Clinical Trials Group or the National Cancer Institute of Canada (NCIC).

Should antibiotic prophylaxis be continued when neutropenic patients become febrile and they go on systemic antibiotics? There seems to be a major disagreement worldwide whether to continue antibiotic prophylaxis or stop it when the patient becomes febrile and goes on systemic antimicrobials. In Canadian clinical trials, we have endeavored to stop prophylaxis since it could be construed as additional therapy and 'muddy the waters' for interpreting the results of the empiric therapy being tested. However, many investigators worldwide do not consider this and continue prophylaxis, feeling that, despite starting systemic therapy, the prophylactic regimen may prevent superinfection or subsequent infection. This could also be pursued either through the CIDS Clinical Trials Group or the NCIC.

G or GM colony stimulating factor (CSF) versus oral antibiotic prophylaxis (versus placebo) in patients with solid tumours undergoing chemotherapy: Both G and GMCSF preparations have been marketed in the United States and certainly will be in Canada within the next year or so. It is expected that in the United States it will become standard practice to use one of these preparations in all solid tumour patients expected to become neutropenic. This could be a huge financial burden to the health care system, both from the cost of the drug and to have to arrange for a nurse in the community to administer the drug. Additionally, it will be difficult to interpret febrile episodes as the preparations are associated with fever. It is likely that a quinolone would be used as the antibiotic prophylaxis in this population if such a study were to take place. The antibiotics are very likely to be cheaper and less difficult to administer. This trial is already being discussed by the NCIC Clinical Trials Committee and will be pursued further by the Infectious Disease Subcommittee (chaired by Dr Feld) during the April 1991 meeting.

LOWER PRIORITY STUDIES

Empiric triazoles (oral or intravenous) versus amphotericin B as empiric therapy for continued fever on day 7 in febrile neutropenic patients: It was felt that the choice of imidazole might be difficult at this time and that it might be a difficult trial to carry out.

Amphotericin B plus GMCSF versus amphotericin B alone in hepatic candidiasis and aspergillosis: There are data suggesting that macrophages may play a significant role in fungal infections, particularly in hard to treat ones such as hepatic candidiasis and aspergillosis. A trial could be designed to address that issue. The major difficulty would be getting a sufficient number of cases to test the hypothesis.

Prophylactic antifungals: A trial might test placebo or nystatin versus a triazole. The endpoints could consist of thrush (with expected improved 'quality of life' when thrush is absent); the need for empiric antifungal therapy due to continued fever (usually amphotericin B) and the frequency of proven fungal infections. The problem with this study is which imidazole to chose and whether a three arm trial is feasible. As well, one would have to control for antibacterial prophylaxis given to avoid superinfections with fungi unrelated to the prophylactic antifungals tested.

Other studies: There was very little interest in looking further at monotherapy, vancomycin, etc, or empiric therapy. There was no interest in looking at antiviral therapy; however, there was some interest in identifying prognostic factors that predict for poor outcome in febrile neutropenic patients. This is being done by Dr Feld using the ceftazadime versus tobramycin-piperacillin patient database. If a model arises from this, it could then be validated on other data sets to see if particular factors can be identified that predict for poor outcome and hence which patients might require different types of therapy. This analysis might also help in stratification in future studies.

SUGGESTED READING

1. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis 1990;161:381-96.
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5. Rubin M, Hathorn JW, Pizzo PA. Infectious complications of cancer. Cancer Invest 1988;6:167-84.