Preventative use of antifungal drugs in patients treated for cancer

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Prophylactic use of antifungal compounds has more or less become standard clinical practice for patients who are treated for a haematological malignancy. However, apart from the prevention of infections by Candida species in bone marrow transplant recipients and a possible reduction in invasive aspergillosis in high-risk patients, there is little evidence to justify this approach. Antifungals ought to be administered to patients on their perceived individual risk and better studies should be conducted to provide a more rational basis for our clinical decisions. Results of studies in specific populations should not be used to create guidelines for other patient groups or general populations. Antifungals are potentially toxic and overuse might be associated with unnecessary direct and indirect drug-related costs.

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Introduction

Prescription of antifungal compounds to prevent the development of an invasive fungal infection during neutropenia eases the physician’s apprehension, engenders a feeling of safety in the patient and increases the sales of pharmaceutical companies. Everybody happy? No? What is the problem?

In fact it is mere frustration: invasive fungal infections are difficult to diagnose. Quite often they are only discovered at autopsy as a major cause of unexplained morbidity. Therefore, it is not surprising that attempts to prevent the occurrence of these infections gained popularity. Unfortunately, in spite of having randomized more than 7000 patients in numerous clinical trials, there is still no solid scientific basis for universal use of antifungal prophylaxis during bone marrow suppressive treatment for a malignant disease.1 Obviously, this is rather different from what had been anticipated by the investigators at the time of the design of the studies. Their disappointment is accentuated by the extensive explanations in the discussion sections in their papers on these trials for the failure to show any benefit. To make it worse, even trials that at first glance appear to provide a positive answer do not survive fastidious dissection.

If there was only one, single study with enough power to validate the principle of antifungal prophylaxis, we could concentrate on the next question and be spared the futile debates between specialists with colliding opinions. There are none. So, must we do new trials? Absolutely, but only after spending ample time at the drawing board designing a study for which all parties—physicians, regulatory authorities, healthcare providers and pharmaceutical companies—take responsibility.

Clinical trial data on antifungal prophylaxis so far

More than 20 years ago, the rationale for antifungal prophylaxis appeared persuasive enough to initiate clinical trials. However, as a result of the poor tolerance of orally administered polyenes in conjunction with their limited efficacy, this approach can, to paraphrase Oscar Wilde, best be described as the inedible in hot pursuit of the unbearable and has to be considered obsolete.2

The paper by Goodman and colleagues3 on fluconazole given as prophylaxis to bone marrow transplant recipients set the trend. Although fluconazole did not influence the overall mortality, the reduction in the incidence and severity of fungal infections fostered its use for prophylaxis in all categories of patients. Such a policy appeared endorsed by an improved overall survival registered in a subsequent, similar trial.4 Disappointingly, even 38 comparative trials were not enough to establish the unequivocal impact of fluconazole on candidiasis-related mortality. Since most trials were statistically underpowered, a meta-analysis was required to grant the label of evidence-based medicine to what already had become common practice.5,6 It is now clear that fluconazole decreases overall mortality in certain subsets of patients who are treated for acute leukaemia, and in stem cell transplant recipients, particularly in cases of prolonged neutropenia.1,5,7 With the role of fluconazole as a prophylactic agent clarified, this leaves the question of dosing. The official registration refers to 400 mg daily, the dosage used to cover Aspergillus species during the initial, successful trials; subsequent studies suggest that lower doses suffice for Candida species.8–10

After a tentative start with negative clinical trials,10 both British and American investigators found that itraconazole protected neutropenic patients better against invasive aspergillosis than did fluconazole.5,11 Unfortunately, the difference in infections due to Aspergillus species...
in the British trial related to an outbreak at one institution, and the Americans had to report a remarkably high incidence of 25% of proven invasive fungal infections in those given fluconazole, presumably as a consequence of a higher proportion of patients who received a stem cell transplant from an unrelated donor and needed excessive amounts of corticosteroids. These observations indicate that prophylaxis is warranted and cost-effective when the prevalence of invasive aspergillosis is high. In addition, the effectiveness of itraconazole in preventing serious fungal infections was shown beyond doubt in an elegant, randomized, cross-over study in patients with chronic granulomatous disease.\textsuperscript{12}

Apart from genuine, technical, clinical trial issues, it is easy to understand why mould infections are much more difficult to prevent than are infections caused by yeasts. Haematogenous candidiasis is supposed to be preceded by colonization of the gastrointestinal tract, followed by dissemination of the organisms after immunosuppression and mucosal damage caused by cytotoxic therapy. Orally administered fluconazole both reduces the Candida burden in the gut and eliminates the organisms after they have gained access to the bloodstream. Mould infection is principally airborne, and oral itraconazole will not eradicate Aspergillus spores and conidia from the airways. In this setting, itraconazole fully depends on its systemic activity, which is probably suboptimal given the poor subjective tolerance. The presumption about the main portal of entry leads us to explore the role of the inhalant form of amphotericin B in the prevention of colonization of the airways by moulds. Amphotericin B aerosol particles are supposed to travel the same route as Aspergillus conidia. The hypothesis is appealing, but in the only prospective randomized trial on this subject there was no significant difference in the incidence of invasive aspergillosis, or in overall survival between patients who received inhalations and those who did not.\textsuperscript{13} Moreover, intolerance forced about one-third of patients to discontinue inhalations prematurely.

The interest in low doses of intravenous amphotericin B, such as 0.10 mg/kg daily or 0.5 mg/kg three times a week, or liposomal amphotericin B, 3 mg/kg 3 days a week, is astonishing. Although the lack of success of itraconazole is commonly attributed to the impossibility of achieving satisfactory serum and tissue levels, some investigators felt compelled to test a homoeopathic dose of amphotericin B. Of course, none of the trials rendered any objective evidence on the efficacy of this approach. At best, it appeared to reduce the need for empirical administration of intravenous amphotericin B. If lower toxicity constitutes a valuable argument to use a suboptimal dose of amphotericin B for prophylactic purposes, abandoning this type of prophylaxis completely to avoid all toxicity would be the next logical step.

**Trial design in the past and the future**

There is a foremost confounding factor that limits the usefulness of the trials, conducted hitherto, on the prophylactic administration of antifungal agents. This is: insufficient sample size—many results are converted into an insignificant finding as a consequence of a type II error. Depending on the incidence in a given study population, 100–1000 patients per arm would be required to prove, with sufficient power, that a difference found in a given trial did not just occur by chance. In addition, in most trials too many patients with a low risk of an invasive fungal infection were enrolled as a result of wide entry criteria. They dilute the population and preclude a firm conclusion. Whereas nobody would think of expanding a trial on malaria prophylaxis to Iceland in wintertime, enrolment of patients with short episodes of neutropenia is quite common. This phenomenon—in combination with the difficulty of ascertaining the presence of an invasive fungal infection—is also the explanation for the belief in home-brewed prophylactic regimens.\textsuperscript{14} Other sources of confusion are the exclusion of critically ill patients and the initiation of empirical antifungal therapy as parameters of outcome. The latter constitutes a poor, anxiety-sensitive, subjective criterion that permits an assessment of the self-confidence of the investigator rather than a conclusion on the efficacy of a prophylactic regimen. Finally, the term invasive fungal infections as a major endpoint was not helpful and never will be. We need to know the efficacy of a regimen against Candida species, Aspergillus species or both.

In future trials, questions on safety and efficacy of a specific antifungal drug should not be mixed with those on the feasibility and value of a given prophylactic strategy. It is time to focus on the latter and therefore it is crucial to select appropriate, high-risk study populations with stratifications to ensure an equal distribution of risk factors. This approach makes it easier to interpret the data.\textsuperscript{7} In the bone marrow transplant study by Winston and associates,\textsuperscript{11} their more homogeneous study population, with its higher intrinsic risk of Aspergillus infections, made itraconazole look more convincing as a possibly protective agent than in all previous trials that had included many patients at low risk.\textsuperscript{5,8,9,15,16} When designing a trial it is important to identify the period during which this risk is highest. This will not automatically coincide with the presence of neutropenia. If one fails to accommodate for confounding events, such as graft-versus-host disease and physical inability to comply with a regimen, several key factors, such as the use of corticosteroids and drop out rates of more than 20%, respectively, may be overlooked.\textsuperscript{11} Preferably, entry criteria should only permit recruitment of naive or meticulously screened patients to exclude the possibility of entering individuals with concealed fungal disease. Ideally, they should be kept in the study until completion of the treatment for their underlying illness.\textsuperscript{10}

Primary and secondary endpoints should be described clearly so that the results of a particular study can be compared with those of other trials and be translated into guidelines for daily practice. Proven and probable invasive candidiasis and aspergillosis, fungus-attributable mortality and overall mortality are objective criteria that permit a thorough evaluation of the strategy or drug under test.\textsuperscript{17}

**Guidelines for clinical practice in neutropenic patients**

Why this open polemic against the widespread use of antifungal prophylaxis? Firstly, practising medicine ought to be evidence-based whenever possible and, secondly, we should adhere to a longstanding principle in medicine: *primum non nocere*, which means that above all we should not inflict damage. One has to realize that none of the presently available antifungal agents is absolutely safe.\textsuperscript{18}

The use of fluconazole prophylaxis is warranted to protect high-risk patients against acquiring an invasive candidiasis.\textsuperscript{1,7,18} The target population consists of allogeneic bone marrow transplant recipients and other patients with protracted neutropenia in combination with mucositis. Additional risk factors are the use of broad-spectrum antimicrobials or corticosteroids and the presence of a venous access device. Based on previous findings it appears that fungal surveillance cultures can be used to determine the subset of patients who are most likely to develop haematogenous candidiasis.\textsuperscript{19}

Treatment for graft-versus-host disease and cytomegalovirus disease puts patients at risk for invasive aspergillosis. Such patients are best protected by itraconazole or voriconazole if concomitant medication does not preclude their use.\textsuperscript{9}
Secondary prophylaxis is a completely different matter. Patients with a proven or probable invasive aspergillosis or candidiasis run a high risk when they undergo further cycles of chemotherapy. Reactivation rates as high as 50% have been reported. In the odd case that aspergillosis is confined to one or a few lung lesions, excision has been recommended; others should receive a therapeutic dose of a systemically active antifungal when the next course of chemotherapy is started. Continuation of prophylaxis after recovery from neutropenia seems not to be indicated unless there is persistent and profound immunosuppression, such as in bone marrow transplant recipients with graft-versus-host disease.

The cornerstones of the success of an individually tailored prophylaxis in patients who are treated for a malignant disease or who are undergoing bone marrow transplantation are an understanding of the temporal sequence of subsequent microbial events, and the employment of laboratory tests and imaging techniques that help to identify patients at risk. On the other hand, the improved diagnostic tools may render prophylaxis redundant because they enable, in conjunction with careful clinical observation, a timely institution of appropriate preemptive antifungal therapy.

References


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