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Meeting Highlight

3rd Biannual Meeting: "Trends in Invasive Fungal Infection"

THE BIENNIAL meeting "Trends in Invasive Fungal Infections 3" was held in Brussels from 7 to 9 September 1995. During the meeting, many presentations were made on the management of fungal infections in cancer patients. Of some concern, were reports that indicated an increasing incidence of unusual fungal pathogens in cancer patients; for instance, a recent survey by the EORTC's Invasive Fungal Infection Cooperative Group identified such strains in 22 out of 270 cases with fungaemia. It has been commonly believed that fungaemia caused by yeasts and invasive candidiasis were almost exclusively the result of endogenous proliferation and invasion in patients without central venous catheters, but increasing evidence points at the possibility of exogenous sources, such as the hands of health care professionals. Another striking observation was the increase of breakthrough fungaemias in patients already receiving empiric antifungal therapy.

John Rex provided details of a major randomised study which compared conventional amphotericin B with fluconazole in patients with candidaemia. Ocular lesions consistent with endophthalmitis were encountered in 15% of patients, which was considered to be strong evidence for routine fundoscopy in patients with, or suspected of, a fungaemia. The final results of this therapeutic trial showed that fluconazole offers a safe alternative to amphotericin B, at least in fungaemias caused by *Candida albicans* in non-neutropenic patients. Yet, removal of a catheter, whenever possible, appeared to be a key issue for a favourable outcome.

The association between risk factors and outcome were also stressed by John Edwards, reporting on the unexpectedly high incidence of yeast infections caused by non-*Candida* species. The risk factors may be institutionally dependent, particularly in some epidemiological circumstances. Moreover, he demonstrated a relationship between carriage of yeasts on the hands of health workers and common isolates in a given institute or unit by means of DNA typing of pathogenic strains. Indeed, 35-75% of nurses were shown to carry *Candida* species on their hands. However, the risk of invasive candidiasis is often unpredictable in cancer patients since approximately 50% of cases with candidaemia had negative surveillance cultures.

His data on the increasing incidence of non-*albicans* candidaemia and institutional clustering were corroborated by Claudio Viscoli who was the co-ordinator of the first large European survey on 270 cases of fungaemia in cancer patients. This study was conducted under auspices of the EORTC's Invasive Fungal Infection Cooperative Group in cancer patients from 30 centres throughout Europe. A registered mortality rate of 40% within 1 month following the positive blood culture for yeasts was comparable to that reported by major centres in the U.S.A.

Breakthrough fungaemia during chemoprophylaxis or empiric antifungal therapy was a commonly observed clinical entity. *Candida tropicalis* fungaemia carried the highest mortality which amounted to 60%. Another dismal parameter was the presence of shock which, under normal circumstances, is rarely primarily associated with candidaemia in the differential diagnosis of such cases. Considering the likelihood of candidaemia remains, therefore, of paramount importance in obtaining a proper diagnosis in patients who are treated intensively for a haematological malignancy or solid tumour.

Robert De Bock called attention to the ongoing study of the EORTC's Invasive Fungal Infection Cooperative Group which compares fluconazole with itraconazole for oropharyngeal candidiasis in cancer patients. This trial represents the first direct comparison of these triazoles in order to establish their respective roles in the treatment of a condition which may precede disseminated candidiasis, especially in immunocompromised patients.

In the field of prevention and chemoprophylaxis of fungal infections in neutropenic patients with cancer, personal and environmental hygiene is still the mainstay, as there is no consensus with regard to optimal agent or recommended dose. A wide dose range, varying from 50 to 400 mg per day, of fluconazole has been used in a prophylactic setting but no clear dose-effect relationship could be ascertained for this drug that constitutes the most extensively tested compound in this area. Since fluconazole offers no protection against aspergillosis, centres with a high incidence of these infections have to consider other options. However, neither the data on the prophylactic use of amphotericin B, either orally or by aerosol or at a low dose intravenously, nor those on itraconazole (with the currently available preparation) or nystatin, are encouraging. For institutions with an excess of invasive candidiasis, fluconazole could be, at least in part, a solution to the problem, particularly in individuals with a substantial amount of *Candida albicans* in their surveillance cultures. On the basis of the data available from randomised studies, a dose of 200 mg per day seems to be acceptable in Europe.

Marc Boogaerts described the indications and strategy for empiric antifungal therapy. As yet, the most appropriate time to initiate empiric treatment with systematically active antifungal agents remains obscure, partly due to the lack of adequate data on this subject, and partly because the majority of persistently febrile neutropenic patients do not suffer from an occult fungal infection. Hence, when such an intervention is deliberated, the balance between the risks and possible benefits of systemic antifungal therapy should be considered. More careful studies are required to define which group of patients would benefit from an empiric approach and to appraise the optimal time to

begin the antifungal drugs. Treatment of a documented fungal infection constitutes a major challenge, especially where there is concomitant granulocytopenia, where the outcome is dismal that all reservations concerning intrinsic adverse effects of empiric administration of antifungal drugs are irrelevant until more effective therapy has been developed or until the risk groups have been better defined.

Koen Torfs presented information on economical aspects of the treatment of fungal infection in cancer patients and described the tools to assess the related costs, including widespread use of expensive formulations of Ambisome or growth factors.

Fritz Offner reviewed the indications for and influence of haematopoietic growth factors in invasive fungal infections. Once again, the need for more data on their efficacy in patients with a documented fungal infection was apparent. The results from the clinical situation are somewhat confusing since, before the fungal infection emerged, most patients already had been treated with a growth factor for other purposes. A careful cost-benefit analysis by means of prospectively randomised clinical trials, with a stratification for documented fungal infections is mandatory in patients with prolonged and profound neutropenia. Such an investigation should include an assessment of the impact of the employment of growth factors on long-term survival. So far, no significantly improved survival has been reported, indicating that there is a need for better definition of patients with a proven or presumed fungal infection who might benefit from the administration of growth factors. None of the studies hitherto have established a role for the haematopoietic growth factors in a prophylactic setting and it seems obvious that they cannot substitute for phagocytic cells. Finally, it was mentioned that there are still concerns about unrestricted use of haematopoietic growth factors in patients with acute non-lymphoblastic leukaemia.

Elias Anaissie, however, found an original way to use haematopoietic growth factors to improve the prognosis of patients with a therapy-refractory documented invasive fungal infection. He pretreated healthy donors with growth factors and, not surprisingly, the harvest by leucopheresis yielded unequaled high numbers of white cells that could be given successfully to patients.

Overall, the aim of this international meeting was to provide a platform for scientific exchange, to supply up-to-date information and to stimulate informal discussions between interested colleagues. This goal was accomplished by a multidisciplinary approach of epidemiology, diagnostic tools, and actual clinical

issues, including new antifungal agents and innovative therapeutic strategies. All these items were discussed by leaders in the field and it became clear that, although substantial progress has been made during the last decade, we are left with more questions than answers. Several controversial issues regarding diagnostic procedures, supportive measures, and therapeutic and prophylactic interventions urgently need to be addressed by clinical investigators in close co-operation with microbiologists and mycologists involved in the care of patients at risk of, or suffering from, fungal infections.

A follow-up meeting, of which the location remains to be determined, has been planned for 1997, where hopefully some answers to the most vital questions of today will be given. For this purpose, clinical trials with an adequate number of patients and proper definitions of risk factors have to be designed and conducted. Multicentre co-operation, providing independent and objective evaluation, is essential to allow sufficient recruitment, and to avoid results that have too low a statistical power to produce generally applicable guidelines for the treatment of patients with fungal infections. If this cannot be accomplished, doctors will have to continue to rely upon data that are at best suggestive, or on assumptions, or intuition.

Facing the challenge of fungal infections in neutropenic cancer patients, a new EORTC cooperative group was created in 1991. The aims of this Invasive Fungal Infections Cooperative Group are: (i) to conduct, develop, coordinate and stimulate research on the epidemiology, diagnosis, prevention and treatment of invasive fungal infections which constitute a real life-threatening infectious complication in patients who are treated for a malignancy; (ii) to increase the awareness of physicians, nurses and all other health care workers with regard to the morbidity and mortality associated with invasive fungal infections; (iii) to provide insight in the economical burden originating from fungal infections to the society and health care systems.

Such international cooperation is required to guarantee a high quality of clinical research in this difficult field of assessing optimal strategies. Any information on clinical research or ongoing activities of the EORTC's Invasive Fungal Infections Cooperative Group can be obtained from Ann Marinus, data manager of the group at the EORTC Data Centre (83, Ave E. Mounier, B-1200 Brussels, Belgium, Tel.: +32-2-774 16 54; Fax: +32-2-772 35 43.)

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