

RISK FACTORS OF BREAKTHROUGH INVASIVE FUNGAL INFECTION (IFI) UNDER SECONDARY PROPHYLAXIS (SP) → MULTINATIONAL EUROPEAN STUDY OF THE ID WORKING GROUP OF THE GERMAN SOCIETY FOR HEMATOLOGY AND ONCOLOGY

Cornely OA, Bethe U, Sieniawski M, Bohme A, Reuter S, Reichert D, Maschmeyer G, Ullmann AJ, Karthaus M, Buchheidt D, Martino R, Einsele H, Haas A, Jedrzejczak W, Silling G, Ohler L, Schiel X, Auner H, Glasmacher A, Kruger W, Gratwohl A, Sandherr M, Klinikum de Universitaet, Koeln, Germany

Background: With the advent of novel less toxic compounds, fungal infections are treated with more success. Chemotherapy can now even be resumed despite prior proven IFI. The need for SP evolved without prior systematic analysis of risk factors for breakthrough IFI or without defining the population at risk.

Methods: We conducted an ongoing survey in 41 tertiary care centers in on SP regimens currently applied. Multilingual case report forms were accessible via www.neutropen.de. Inclusion criteria are: leukemia or lymphoma, proven/probable IFI according to EORTC/BAMSG during the most recent neutropenic episode (E1), and planned to undergo a next neutropenia (E2).

Results: As of Jan 31, 2003, 169 evaluable pts were included: age 11-88, median 46y, 41% female, 82% AML. Proven IFI (35.5%) in E1 were 39 (23%) aspergillosis, 12 (7.1%) candidiasis, 4 (2.4%) mucormycosis, and geotrichosis, hyalohyphomycosis, trichosporosis, fusariosis and other mycosis in 1 (0.6%) each; probable IFI (64.5%) in E1 involved the lungs in 102 (60.4%) pts, lungs/liver in 4 (2.4%), liver alone, liver/spleen, and lungs/sinus in 1 (0.6%) each.

SP in E2 contained of amphotericin B iv in 60 (35.5%), itraconazole in 91 (53.8%), voriconazole in 10 (5.9%), fluconazole in 13 (7.7%), caspofungin in 9 (5.3%), posaconazole in 1 (0.6%), flucytosine in 1 (0.6%), and none in 22 (13%) patients. Incidences of proven/probable/possible breakthrough IFI under SP among 60 amphotericin B pts were (3/9/5, i.e. 28%), among 91 itraconazole pts (3/11/10, i.e. 26%), and among all (8/24/16, i.e. 28%). Proven IFI in E2 were aspergillosis in 5, and candidiasis, fusariosis and aspergillosis with candidiasis in 1 patients each; probable IFI in E2 involved the lungs in 18, liver in 2, lungs/liver in 2, lungs/spleen in 1 and lungs/CNS in 1 pts; possible IFI accounted for 16 pts. Death occurred in 20 (12%) pts and was attributable to IFI in 6 (4%) pts.

Applying logistic regression for the analysis of possible risk factors revealed that the use of steroids of >2mg/kg for >7d is the only highly significant risk factor for breakthrough IFI ($p < 0.001$). In our model risk factors without statistical significance are the following: laminar air flow, HEPA filter, construction work, remission status of the underlying malignancy, duration of neutropenia, mucositis grade, diabetes mellitus, central venous catheter, parenteral nutrition, cytostatics chosen, anti-lymphocyte antibodies, number of antibiotics, and number of days on antibiotics.

Conclusions: SP after proven or probable IFI is instituted frequently and with various regimens. The incidence of breakthrough second IFI and crude mortality is high in this population. Use of high dose steroids increases the risk for breakthrough IFI. Prospective studies on secondary prophylaxis and risk factors for breakthrough IFI are urgently warranted.