Azole-Resistance in *Candida* infections and induction by cytotoxic agents

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*Candida* spp. infections have increased in incidence among immunocompromised patients in recent years and have now become the fourth most common bloodstream infection. This pathogen poses a serious threat to chemotherapy patients whose immune system is compromised by leukemia or other types of cancer. Some molecular processes are linked to the emergence of intractable fluconazole-resistant *Candida albicans* infections. The most important mechanisms associated with resistance development are: 1) upregulation of CDR1 and CDR2, genes encoding multidrug efflux transporters of the ATP-binding cassette (ABC) transporter family, 2) upregulation of MDR1, a major facilitator transporter gene, and 3) transcription increase of ERG11, a gene coding for the drug target enzyme sterol 14 α-demethylase or ERG11 point mutations. The transporter proteins increase active efflux of antifungal agents, and upregulation of ERG11 increases the amount of the target enzyme, making the intracellular azole concentration insufficient to inhibit the enzyme activity.

Multidrug resistance (MDR) of neoplastic tissues is a persistent problem in cancer chemotherapy. The main cause of MDR is overexpression of P-glycoprotein (P-gp), a member of the human ABC transporter family. This transporter family has broad substrate specificity for several substances, including anticancer drugs, linear and cyclic peptides, HIV protease inhibitors, and several other molecules.

We examined whether cytotoxic drugs commonly used for cancer treatment (doxorubicin and cyclophosphamide) could alter the expression of genes responsible for the development of fluconazole resistance in Candida cells in the way they can influence homologous genes in cancer cell lines. ABC transporters (CDR1 and CDR2) and other resistance genes (MDR1 and ERG11) were tested by real-time PCR for their expression in *C. albicans* cells at the mRNA level after induction by antineoplastic drugs. The results were confirmed by a lacZ gene reporter system and verified at the protein level using GFP and immunoblotting (1;2).

Reference List
Markus Ruhnke, M.D., is a Professor of Medicine in the Department of Medicine, Division Oncology & Haematology at the Charité University Hospital Campus Mitte Berlin and currently serves as the vice-chairman of the Dep. of Medicine, Div. Oncology & Haematology. He graduated at the Free University Berlin in 1982, received a diploma in tropical medicine & hygiene (DTM&H London) in 1990 and has been trained in infectious diseases and haematology and oncology at the Charité University Medicine in Berlin. Since 1997 he is a consultant for clinical mycology and infectious diseases as well as a lecturer in haematology and oncology. In 2009 he became Professor for Mycology in Oncology of the "Deutscher Stifterverband". Professor Ruhnke's research interests include molecular diagnosis, pathogenesis and therapy of fungal infections in immunocompromised hosts.

Professor Ruhnke is principal and coordinating investigator of several clinical trials focusing on treatment and diagnosis of invasive fungal infections as well as member of several international advisory boards on antifungal agents.

Professor Ruhnke is a member of several national and international societies including the European organisation for research and treatment of cancer (EORTC) and the European confederation on Medical Mycology (ECMM). He is past-president of the German-speaking Mycological Society (DMykG e.V.).

He has edited and authored numerous book chapters on fungal infections as well as over 130 articles in leading peer-reviewed journals such as Lancet, Blood, Clinical Infectious Diseases, Journal of Clinical Microbiology, Antimicrobial Agents & Chemotherapy, Journal of Antimicrobial Chemotherapy, and Drugs and has been a Journal reviewer for publications as the Journal of Antimicrobial Chemotherapy, Haematologica, European Journal Infectious Diseases and Clinical Microbiology, Clinical Microbiology and Infection, Diagnostic Microbiology and Infectious Diseases. He serves as editor ex officio DMykG for the journal "mycoses" and belongs to several editorial boards ("Journal of Microbiology, Immunology and Infection", "Current Fungal Infection Reports.", "Open Mycology").

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