Abstract: Predicting the unpredictable. Individual risk stratification of patients at risk of IA

The incidence of invasive aspergillosis (IA) in high risk haematology populations, is relatively low (<10%), despite unavoidable exposure *Aspergillus* in patients with potentially similar clinical risk. Non-clinical variables including genetic mutations that increase susceptibility to IA could explain why only certain patients develop disease. This study aimed to screen for mutations in 322 haematology patients classified according to IA status, and to develop a predictive model based on genetic risk, established clinical risk factors and diagnostic biomarkers.

Genetic markers were determined by real-time PCR, and with clinical risk factors and *Aspergillus* PCR results were analysed by multi-logistic regression analysis to identify a best-fit model for predicting IA. Probability of IA was calculated and an optimal threshold determined.

Mutations in Dectin-1 (rs7309123) and DC-SIGN (rs11465384 and rs7248637), allogeneic stem cell transplantation, respiratory virus infection and *Aspergillus* PCR positivity were all significant risk factors for developing IA and combined in a predictive model. An optimal threshold requiring three positive factors generated a mean sensitivity/specificity of 70.4%/89.2%, and a probability of developing IA of 56.7%. In patients with no risk factors the probability of developing IA was 2.4%, compared to >79.1% in patients with four or more factors. Using a risk threshold of 50%, pre-emptive therapy would have been prescribed in 8.4% of the population.

Summary

This pilot study shows that patients can be stratified according to risk of IA, providing personalized medicine, based on strategic evidence, for the management of IA. Further studies are required to confirm this approach.