Effect of voriconazole resistance on mortality in invasive aspergillosis: a multicentre, retrospective, cohort study

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Background: Triazole resistance is an increasing problem in invasive aspergillosis (IA) and complicates patient management. Case series show mortality rates of 50% to 100% in triazole-resistant IA patients, but comparisons with patients with triazole-susceptible IA are lacking.

Materials/methods: Between 2011 and 2015 all A. fumigatus culture-positive patients in three University Medical Centers were investigated to identify patients with IA. Patients were classified as having putative, probable or proven IA. Clinical characteristics, day-42 and day-90 mortality, voriconazole resistance profile and antifungal treatment were investigated.

Results: A total of 200 patients were classified with IA of which 37 had voriconazole (VCZ)-resistant isolates (19%). 79% of patients had received VCZ as first-line antifungal therapy. The overall mortality in VCZ-resistant IA was 18/37 (49%) and 23/37 (62%) at day-42 and day-90, respectively compared with 48/163 (29%) and 62/163 (38%) in VCZ-susceptible IA (Kaplan-meier survival analysis with logrank test at 42 and 90 days, respectively P=0.029 and P=0.007). 28 patients received initial therapy with L-AmB but their survival was not better than VCZ treated patients, both with VCZ-susceptible and VCZ-resistant IA (log-rank test, p=0.047). However, the proportion of patients admitted to the ICU in L-AmB-treated group was significantly higher compared with VCZ-treated patients (21 of 28 (75%) L-AmB-treated patients versus 70 of 157 (45%) VCZ-treated patients; two-tailed Fisher exact test, p=0.0037), indicating that L-AmB therapy was used in patients with more severe infection. In 30 patients voriconazole therapy was started and then switched because of VCZ-resistant IA. The cumulative survival was significantly lower in this group compared with VCZ-treated patients with VCZ-susceptible IA (logrank test at 42 and 90 days, respectively P=0.032 and P=0.010).

Conclusions: VCZ-resistant IA was associated with a significant increased mortality compared with VCZ-susceptible IA. Delay of appropriate antifungal therapy was found to be associated with increased mortality underscoring the need for upfront coverage of resistance in regions with high resistance rates.