Objective: Empirical antifungal therapy is considered the standard-of-care for high-risk neutropenic patients with persistent or recurrent fever of unknown origin. A pre-emptive, diagnostic-driven approach based on serum galactomannan (GM) screening and chest CT-scan might provide a feasible alternative. In this prospective non-inferiority trial, we compared the impact of an empirical antifungal strategy (Arm A) to a pre-emptive strategy (Arm B) in patients with prolonged neutropenia on survival and on the occurrence of invasive fungal diseases (IFD)

Methods: We randomly assigned patients with acute myeloid leukaemia or myelodysplastic syndrome (AML/MDS) and recipients of an allogeneic hematopoietic cell transplant (HCT) admitted to hospital to receive remission induction therapy or to undergo myeloablative conditioning therapy to be managed with either Arm A or Arm B. All patients were to receive fluconazole prophylactically at 400 mg/d. Patients in Arm A were to receive caspofungin for persistent or recurrent fever whereas those in Arm B received the echinocandin only when there was mycological or radiological evidence of an IFD. The primary endpoint was overall survival (OS) 42 days after randomization. Secondary endpoints included OS at day 84, the development of a proven and probable IFD according to the 2008 EORTC-MSG definitions, fungal-free survival, number of days of caspofungin treatment and safety.

Results: Of 556 adults recruited, 549 were eligible: 275 in Arm A, 274 in Arm B. The median duration (Q1-Q3) of neutropenia (ANC <500/mm^3) was 22 days (IQR 18 to 28) in Arm A and 21 days (IQR 17 to 26) in Arm B (p=0.15). Eighty percent of the patients had received high-dose chemotherapy for AML/MDS of which 93% were given it for first remission induction. On day 42, the OS rates were, respectively, Arm

B 96.7%; 95% CI; 93.8 - 98.3 and Arm A 93.1%; 95% CI, 89.3 - 95.5% confirming the non-inferiority of arm B. The rates of IFDs at day 84 were not significantly different [Arm B 7.7% 95%CI, 4.5 – 10.8% versus Arm A 6.6% 95%CI, 3.6 – 9.5%]. However, the number of patients receiving caspofungin in Arm B was significantly lower at 27% than in Arm A at 63%($p<0.001$).

Conclusion: A pre-emptive antifungal strategy based on a twice weekly GM screening and chest CT-scan is safe for high-risk neutropenic patients receiving fluconazole prophylaxis with fewer patients receiving antifungals without any excess mortality or IFDs.

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