

Empirical versus pre-emptive antifungal therapy for persistent febrile neutropenia

We read with interest the paper from Pagano *et al.* regarding the results of a prospective survey on the use of antifungal drugs in adult leukemic patients.¹ In spite of the non-randomized features of the study, the Authors compare patients treated with 2 different strategies: empirical versus pre-emptive antifungal therapy for persistent fever in presence of neutropenia. The most striking results of this comparison are the lower incidence of invasive fungal disease (IFD) in patients receiving empirical therapy and the higher mortality in patients treated pre-emptively. These results are similar to those observed in another randomized study,² but in our opinion in the interpretation of the results of both studies there is the same bias. In fact, while pre-emptive therapy is administered to patients with "something more" than persistent fever, i.e. in the presence of clinical, radiological and sometimes microbiological features suggestive of an IFD, empirical antifungal therapy is administered to patients with "only" persistent fever, and nobody really knows what all these "fevers" are. Therefore, it is not surprising that the incidence of IFD is lower in patients receiving empirical therapy, since an IFD is probably not present in the majority (actually probably in none) of the cases treated empirically. Similarly patients could not have been recorded to die from an infection they actually did not have. On the contrary, the pre-emptive strategy looks for and frequently finds IFD. Therefore, there is a higher probability of dying from an IFD, since the patient is really affected.

Surveys like that of Pagano *et al.* are useful to analyze the toxicity of antifungal drugs in everyday clinical practice (i.e. outside the strict rules of randomized clinical trials), but unfortunately this aspect is not reported in the paper. This type of study cannot, therefore, be used to give therapeutic indications, particularly concerning the highly controversial issue of the use of empirical or pre-emptive antifungal therapy.

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Key words: infectious disorders, invasive mycosis, therapy.

Citation: Castagnola E, Haupt R. Empirical versus pre-emptive antifungal therapy for persistent febrile neutropenia. *Haematologica* 2012;97(1):e1. doi:10.3324/haematol.2011.056077

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