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LETTER TO THE EDITOR

Invasive fungal infections in patients with acute myeloid leukemia and in those submitted to allogeneic hemopoietic stem cell transplant: who is at highest risk?

To the Editor:

Invasive fungal infections (IFIs) are a growing cause of morbidity and mortality in patients with acute myeloid leukemia (AMLs) and in recipients of allogeneic hemopoietic stem cell transplantation (allo-HSCTs) (1–6). It is widely debated if either allo-HSCTs or AMLs are to be considered at higher risk, but no data comparing the two categories of patients have been reported in literature so far.

This cohort study has been conducted from January 1999 to December 2003 in hematology wards located throughout Italy. The study was aimed at evaluating the incidence and mortality for IFIs in adult AMLs and in patients submitted to all types of allo-HSCT procedures; a comparison between the two categories of patients was carried out.

EORTC/MSG consensus criteria were used to define IFIs (7). Only infections that were classified as 'proven' or 'probable' were included in the data analysis. Overall and IFI-attributable mortality rates (IFI-AMR) were estimated. IFI-AMR was defined as a progression of sepsis-related symptoms or of the involved organ failure in the absence of other morbid condition thought to cause death. Outcome was assessed on the 150th day after IFI diagnosis.

During the 5-yr study, 1596 new patients received intensive chemotherapy for AML and 679 were submitted to allo-HSCT procedures in the nine participating centers. Proven or probable IFIs were documented in 270 AMLs (174 moulds and 96 yeasts) (incidence 16.9%) and in 56 allo-HSCTs (43 moulds and 13 yeasts) (incidence 8.2%). All yeast infections were sustained by *Candida* spp. Conversely, mould infections were mostly caused by *Aspergillus* spp (96% in AML and 91% in HSCT); only a few cases due to rare agents were observed.

Significant differences emerged from the comparison of IFI incidence rates in AMLs and allo-HSCTs. The overall mortality rate for fungal infection was 5.9% in AMLs and 5.7% in allo-HSCTs, with an IFI-AMR of 34.8% and 69.6% respectively (Table 1). Furthermore, we separately analyzed mould and yeast infections. In yeast infections, the incidence was higher in AMLs (*P*-value <0.001), while differences in AMR were not statistically significant (*P*-value 0.105). As for moulds, significant differences in both incidence rate and AMR were found in AMLs and allo-HSCTs (*P*-value <0.001).

Data about mortality rate became more impressive after having compared AML patients treated with chemotherapy (174 pts) to those treated with allo-HSCT (21 pts). Mortality reached 90.5% in transplanted patients (RR 2.58, CI95% 2.02–3.3, *P*-value <0.001).

IFIs appeared both during the early and late phase after allo-HSCT. Interestingly in moulds infections only, AMR resulted higher for those infections occurring within 100 d from transplant (AMR 85% in early vs. 56% in late aspergillosis, *P*-value 0.04); it means that patients receiving allo-HSCT continue to be at risk for IFIs even after 100 d, but risk of mortality decreases during the post-engraftment phase.

Table 1 Comparison between AML and allo-HSCT patients in nine centers

	No. cases/No. patients	Incidence (CI95%)	*P*-value	No. exitus/No. cases	AMR (CI95%)	*P*-value
IFIs						
AML	270/1596	16.9% (15.4–19.1)	<0.001	94/270	34.8% (29.2–40.6)	<0.001
Allo-HSCT	56/679	8.2% (6.4–10.5)		39/56	69.6% (56.7–80.6)	
Moulds						
AML	174/1596	10.9% (9.4–12.5)	<0.001	61/174	35% (28.8–43.0)	<0.001
Allo-HSCT	43/679	6.3% (4.7–8.4)		32/43	74.4% (59.9–85.7)	
Yeasts						
AML	96/1596	6% (4.9–7.3)	<0.001	33/96	34.4% (25.4–44.3)	0.105
Allo-HSCT	13/679	1.9% (1.1–3.2)		7/13	53.8% (27.4–78.7)	

IFIs, invasive fungal infections; AML, acute myeloid leukaemia; allo-HSCT, allogenic haematopoietic stem cell transplantation; AMR, attributable mortality rate.

Our data confirm that AML constitutes the category most exposed to the risk of developing an IFI. This is probably due to some host factors; in fact, it is well known that AMLs are frequently colonized by *fungi* at diagnosis because of the daily inhalation of conidia; in such patients fungal agents may become virulent and a systemic dissemination may occur when spores are not cleared out because of the depressed immune defenses (i.e. neutropenia due to bone marrow invasion and chemotherapy). Conversely, patients undergoing HSCT are generally more selected thanks to a good clinical performance status. Furthermore, persistent, profound neutropenia and the breakdown of physical barriers, which represent important risk factors for IFIs, occur in almost all AMLs undergoing intensive chemotherapy; on the contrary, acute and chronic GVHD, the major risk factor for IFIs in allo-HSCTs, develops only in a part of patients depending on the particular transplant procedure they are submitted to.

IFI-AMR was significantly higher in allo-HSCTs, particularly in patients developing moulds infection within 100 d from transplant. Differences in outcome are probably related to the treatment intensity, the coexistence of other complications (i.e. GVHD and steroid therapy, CMV disease), the use of antifungal prophylaxis and the immunosuppression complexity and duration. In fact, the recovery of immune impairment after allo-HSCT procedures occurs late and depends on the use of immunosuppressive agents required for the treatment of GVHD, while the recovery of chemotherapy induced neutropenia usually occurs within a few weeks or days and represents the major factor influencing the outcome of IFIs in AMLs.

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