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P2275 Voriconazole prophylaxis in allogeneic haematopoietic stem cell transplant recipients and hepatotoxicity

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Background: Voriconazole (VCZ) antifungal prophylaxis (AFP) is frequently discontinued in allogeneic hematopoietic cell transplant recipients (allo-HCTr) due to toxicities. We reviewed predictors of VCZ discontinuation and hepatotoxicity in allo-HCTr who received VCZ-AFP.

Materials/methods: Single-center retrospective study of adult allo-HCTr (2014-2016). VCZ-AFP was continued until Day75-180 post-HCT based on individual allo-HCT risk factors, as per institutional standard of care (SOC).

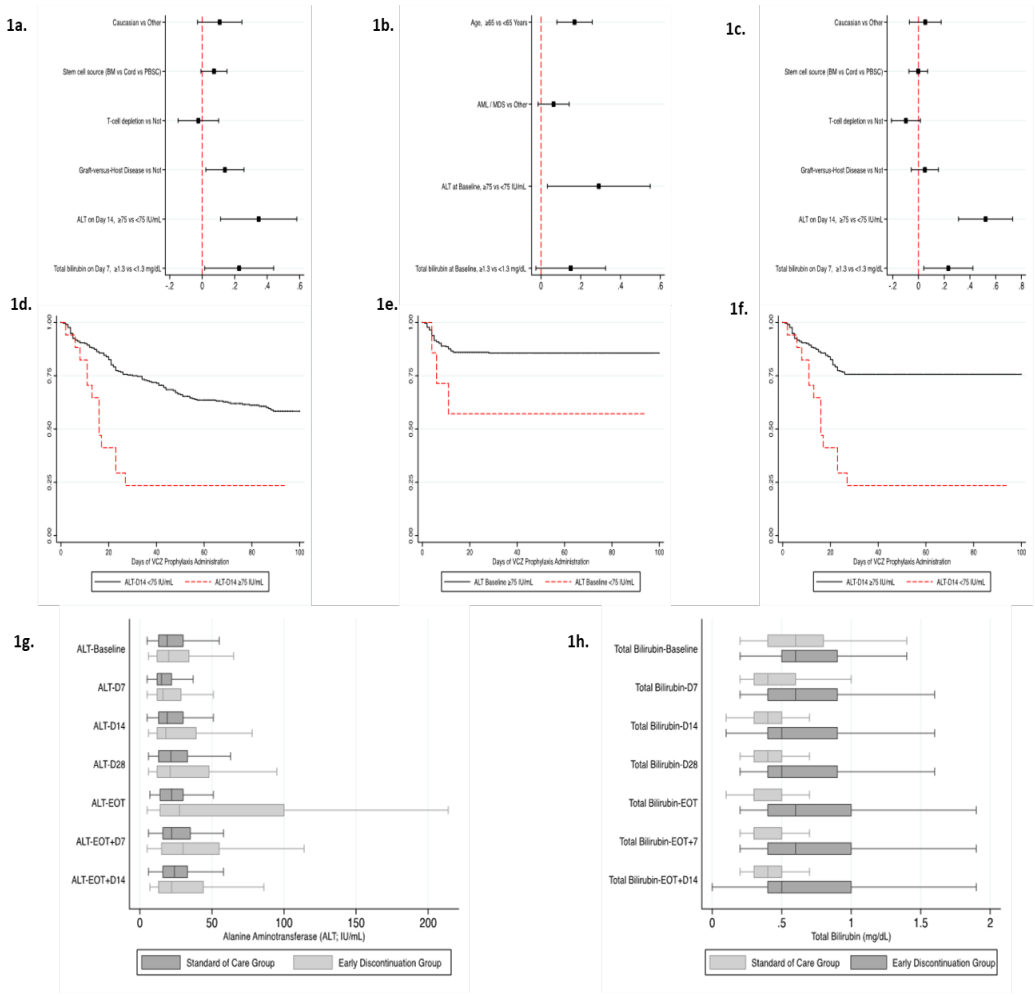
Results: Among 327 allo-HCTr, VCZ was started at a median of 7 days (range:1-43) post-HCT and continued for a median of 69 days (range1-100). VCZ-AFP was stopped in 147/327 (45%) patients (early-VCZ-discontinuation group) at a median of 20 days (range:1-89) after VCZ-AFP initiation vs 90 days (range:2-100) in the SOC-group (*P*-value<0.001). Voriconazole was prematurely discontinued in 101/147 (68.7%), 26 (17.7%), 13 (8.8%) and 7 (4.8%) patients due to: adverse events, drug-drug interactions, insurance coverage and other, respectively. Liver function test (LFT) abnormalities were the most frequent adverse event (73/101;72.3%), followed by visual hallucinations/central nervous system symptoms (16/101;15.8%), skin rash (6/101;5.9%), and other (6;6%).

Predictors of early-VCZ-discontinuation at any time, by Day-14 and Day-28 post VCZ-AFP initiation were studied (Figures 1a, b, and c, respectively). Alanine aminotransferase (ALT) ≥75IU/mL on Day-14 post-VCZ initiation predicted early-VCZ-discontinuation at any point (odds ratio, OR: 5.6, *P*-value:0.02; Figure-1d) and by Day-28 (OR:7.7, *P*-value:0.01; Figure-1f). Baseline ALT≥75IU/mL and age ≥65-years were the strongest predictors of early-VCZ-discontinuation by Day-14 (OR: 5.4, *P*-value:0.04 and OR:3.2, *P*-value:0.001, respectively; Figure-1e). Voriconazole-associated variables (dose/mode of administration) were not associated with early-VCZ-discontinuation.

The mean ALT and total bilirubin values during VCZ-AFP in the early-VCZ-discontinuation and SOC- group are presented in Figures-1g,h. The mean ALT at the end of voriconazole administration was 76.9IU/mL and 38.6IU/mL in the early-VCZ-discontinuation and SOC-group, respectively (*P*-value:0.02). The mean total bilirubin at the end of voriconazole administration was 0.90mg/dL and 0.44mg/dL in the early-VCZ-discontinuation and SOC-group, respectively (P-value<0.001). VCZ-AFP discontinuation resulted in rapid ALT and bilirubin decline by Day-7 and 14 post-VCZ-discontinuation (Figures-1g,h).

Conclusions: VCZ-AFP is frequently discontinued in allo-HCTr. Moderate-degree LFT abnormalities between baseline and Day-14 post VCZ-initiation may predict early-VCZ-discontinuation.

Figure 1.


1a.
Caucasian vs Other
Stem cell source (BM vs Cord vs PBSC)
T-cell depletion vs Not
Graft-versus-Host Disease vs Not
ALT on Day 14, ≥75 vs <75 IU/mL
Total bilirubin on Day 7, ≥1.3 vs <1.3 mg/dL
1b.
Age, ≥65 vs <65 Years
AML / MDS vs Other
ALT at Baseline, ≥75 vs <75 IU/mL
Total bilirubin at Baseline, ≥1.3 vs <1.3 mg/dL
1c.
Caucasian vs Other
Stem cell source (BM vs Cord vs PBSC)
T-cell depletion vs Not
Graft-versus-Host Disease vs Not
ALT on Day 14, ≥75 vs <75 IU/mL
Total bilirubin on Day 7, ≥1.3 vs <1.3 mg/dL
1d.
Days of VCZ Prophylaxis Administration
ALT-D14 <75 IU/mL
ALT-D14 ≥75 IU/mL
1e.
Days of VCZ Prophylaxis Administration
ALT Baseline ≥75 IU/mL
ALT Baseline <75 IU/mL
1f.
Days of VCZ Prophylaxis Administration
ALT-D14 ≥75 IU/mL
ALT-D14 <75 IU/mL
1g.
ALT-Baseline
ALT-D7
ALT-D14
ALT-D28
ALT-EOT
ALT-EOT+D7
ALT-EOT+D14
Alanine Aminotransferase (ALT, IU/mL)
Standard of Care Group
Early Discontinuation Group
1h.
Total Bilirubin-Baseline
Total Bilirubin-D7
Total Bilirubin-D14
Total Bilirubin-D28
Total Bilirubin-EOT
Total Bilirubin-EOT+7
Total Bilirubin-EOT+D14
Total Bilirubin (mg/dL)
Standard of Care Group
Early Discontinuation Group