Development of Anemia and Changes in Hemoglobin Concentrations with Amphotericin B therapy for Cryptococcal Meningitis

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Abstract

Background: Anemia represents a common toxicity with amphotericin B-based induction therapy for HIV-infected persons with cryptococcal meningitis. We sought to examine the impact of anemia-related factors on survival. Methods: Data from Ugandan and South African participants from the COAT and ASTRO-CM trials were used to characterize variation of hemoglobin (Hb) concentrations from diagnosis to 12 weeks post-diagnosis. Anemia severity was classified based on Hb at cryptococcal meningitis diagnosis, and nadir Hb values during amphotericin induction. Cox proportional hazard models estimated 2-week induction period mortality risk among participants with nadir hemoglobin <8.5 g/dL (Grade 3 anemia). All received induction therapy with amphotericin deoxycholate (800 mg/day). Flucytosine (850 mg/day) was administered during amphotericin induction. Results: The median (IQR) nadir hemoglobin concentration during amphotericin induction was 8.4 g/dL (5.9; 9.6) among those who died during the induction period. Anemia severity was classified based on nadir Hb ≤7.4 g/dL (Grade 2 anemia). Cox proportional hazard models estimated 2-week mortality risk among those who died during the induction period. Anemia severity was classified based on nadir Hb ≤7.4 g/dL (Grade 2 anemia). Cox proportional hazard models estimated 2-week mortality risk among those who died during the induction period. Anemia severity was classified based on nadir Hb ≤7.4 g/dL (Grade 2 anemia).

Introduction

• Anemia is an independent predictor of mortality in AIDS patients with an increased risk of death as hemoglobin levels decline.1,2
• Amphotericin, the mainstay of cryptococcal meningitis treatment, has been shown to cause anemia.1,2
• We characterized the relationship between amphotericin administration and hemoglobin levels during and after treatment.
• We also assessed the relationship between hemoglobin levels in individuals receiving amphotericin therapy and 2-week and 10-week mortality.

Methodology

• Data from the Cryptococcal Optimal ART Timing (COAT) trial and the pilot phase of the Adjunctive Sterilization for Treatment of Cryptococcal Meningitis (ASTRO-CM) trial were used for the analysis included herein.
• COAT trial participants were ART-naive at the time of meningitis diagnosis whereas 45% of ASTRO-CM participants were receiving ART.
• Participants were ≥18 years of age, pregnant women were excluded.
• All received combination induction therapy with amphotericin B deoxycholate (0.7-1.0 mg/kg/day) and fluconazole (800 mg/day).
• Adjunctive extracellular (100-400mg/day) was administered to all ASTRO-CM pilot trial participants.
• Participants were followed for at least 12 weeks post-enrollment.
• Serial hemoglobin levels were obtained from participants at baseline and additional intervals through the follow up period.
• Anemia severity was defined as follows: 2

1. Moderate anemia (Grade 2) – hemoglobin ≤7.5 – 8.4 g/dL.
2. Severe anemia (Grade 3) – hemoglobin ≤ 6.5 – 7.4 g/dL.
3. Potentially life-threatening anemia (Grade 4) – hemoglobin ≤ 6.5 g/dL.

Statistical Analysis:

• Median hemoglobin concentration at diagnosis (both cohorts) and 14-day induction therapy nadir values (COAT only) are summarized.
• Change in hemoglobin concentrations from baseline to 1) the end of induction therapy and 2) the 14-day nadir hemoglobin were evaluated via linear mixed models with random intercepts for an individual.
• Composite exposures of grades 2-4 and 3 anemia at baseline were used in Cox proportional hazards models to evaluate 2-week and 10-week mortality.
• Nadir hemoglobin values during induction therapy were used to assess the risk of 10-week mortality among COAT participants with baseline hemoglobin ≤8.5 g/dL and survived 2 weeks.

Conclusions

• For patients with baseline Hgb ≥8.5 g/dL:
  - Hgb dropped by ≥3.5g/dL after 14 days of amphotericin induction therapy.
  - Hgb levels rebounded to 90% of baseline hemoglobin within 10 weeks after the completion of amphotericin.
• Development/worsening of anemia while on amphotericin had no effect on 10-week mortality.

For patients with baseline Hgb ≤8.5 g/dL:
• There was an elevated risk of death at both 2 and 10 weeks post diagnosis when compared to persons with baseline Hgb ≥8.5 g/dL.

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