Infectious complications following allogeneic stem cell transplantation by using antithymocyte globulin-based myeloablative conditioning regimens in children with hemoglobinopathies

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1. Introduction

Antithymocyte globulin (ATG) has been used to prevent graft failure/rejection in the setting of allogeneic stem cell transplantation (allo-SCT) for hemoglobinopathies. The addition of ATG in conditioning regimens has been associated with delayed immune reconstitution and consequently with increased infection rates; however, relevant data are scarce and inconsistent. The objectives of this study were to describe the rates and patterns of infections complicating allogeneic myelo-ablative SCT with ATG-based conditioning regimens, in a homogenous cohort of children with hemoglobinopathies.

2. Methods

This is a retrospective study on the epidemiology of infections in a cohort of 105 children and adolescents with β-thalassemia (n= 100) or sickle cell disease (n=5) who underwent allo-SCT using HLA-identical sibling (n=96) or HLA-compatible unrelated donors (n=9), in a single institution, during the period of November 1995 until June 2013. All patients received an ATG-based conditioning regimen

3. Results

Viral infections

• 48 patients developed at least one episode of CMV reactivation during the first 6 months after transplantatio. The median time of the first CMV-reactivation episode was 40 days (range, 8-156). Five patients had recurrent episodes of CMV-reactivation. All patients were given pre-emptive antiviral therapy with Foscarnet or Ganciclovir
• 8 patients developed localized herpes zoster (HZ) disease. All patients were treated with acyclovir. Median time of HZ occurrence was 12 months (range 8-24 months) after transplant
• 1 patient presented with EBV viremia 1 year post-transplant while he was receiving immunosuppression for cGVHD. Viremia resolved within two weeks after receiving pre-emptive therapy with rituximab
• 10 patients developed hemorrhagic cystitis (HC); 6 patients had at least 1 positive sample for polyoma (BK) viruria tested with PCR for BKV DNA. Median time to onset of HC was 35 days (range, 26-52 days). All patients had a complete clinical response after standard care therapy

Bacterial infections

• During the first 12 months post transplantation, 15 patients developed at least 1 episode of bacteremia. The cumulative incidence of bacteremia is shown in **Figure 1**. The median time to onset of the first bacteremia episode was 13 (range, 1-309) days; 8 cases of bacteremia occurred during the neutropenic phase
• All episodes occurred while patients were receiving ciprofloxacin (n=10) or penicillin (n=5). Gram (+) bacteria were isolated in 9 patients (8 *Staphylococcus aureus* and 1 *Bacillus cereus*) while Gram (-) bacteria were detected in 6 patients (2 *Pseudomonas aeruginosa*, *2 Klebsiella pneumonia*, 1 *Acinetobacter*, and 1 *Argobacterium radiobacter*)

Fungal and parasitic infections

• None of the patients developed probable or proven invasive fungal infection. However, among the 4 deaths in our series, 2 were directly attributed to infections and occurred at 6 and 4 months in the post transplant period at the absence of GVHD
• Disseminated toxoplasmosis and *Pneumocystis jiroveci* pneumonia were the identified causes respectively

Patient and donor characteristics

Characteristic	Value
Median patient age (years)	10.97
Median donor age (years)	10
Female donor/male recipient (%)	31
β-Thalassemia	100
Sickle cell disorder	5
Medium serum ferritin, ng/ml(median, range)	1561 (120-7000)
HLA-identical sibling	96
HLA-identical unrelated donor	9
Donor-recipient CMV status	
Both positive	34
Both negative	37
R/D (+/-)	17
R/D (-/+)	9
Conditioning regimen	
Bu+Cy+ATG	76
Bu+Cy+Flu+ATG	22
Nucleated cell dose x10^8/kg (median, range)	7.4 (1.8-12)

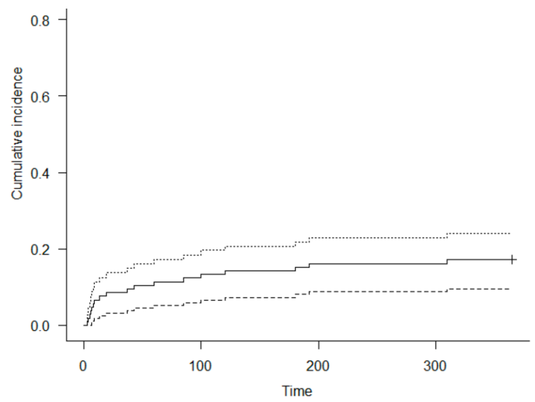

Figure 1. Cumulative incidence of bacteremia (median, 95% CI)

4. Conclusion

✓ **The profile, incidence and timing of infections observed in children transplanted with ATG-based conditioning regimens for hemoglobinopathies, seem to be comparable with those observed with non ATG-based regimens. Taking our data into consideration we can assume that the beneficial effect of ATG on engraftment and GVHD is not compromised by an increased rate of infections.**