J Pediatr (Rio J). 2014;90(5):523–527

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

Outcome of children with severe acquired aplastic anemia treated with rabbit antithymocyte globulin and cyclosporine A☆,☆☆

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Received 15 July 2013; accepted 17 February 2014
Available online 27 May 2014

KEYWORDS
Aplastic anemia;
Immunosuppressive therapy;
Anti-thymocyte globulin;
Pancytopenia;
Relapse;
Clonal evolution

Abstract
Objective: To evaluate the outcome of children with severe acquired aplastic anemia treated with rabbit antithymocyte globulin and cyclosporine as first-line treatment at this institution.
Methods: Retrospective analysis of 26 pediatric patients with aplastic anemia, treated between 1996 and 2011 with rabbit antithymocyte globulin plus cyclosporine.
Results: The overall response rate at six months was 34.6% (9/26), and the cumulative incidence of relapse was 26.5% (95% confidence interval [CI]: 1.4%-66%) at 5 years. The cumulative incidence of clonal evolution after immunosuppressive therapy was 8.3% (95% CI: 0.001%-53.7%) at five years with both clonal evolutions in non -responders who acquired monosomy 7 karyotype. The overall survival at five years was 73.6% (95% CI: 49.2%-87.5%).
Conclusions: The present results confirm the poor response rate with rabbit antithymocyte globulin as first therapy in pediatrics patients, similar to what has been reported for patients of all ages. This confirmation is problematic in Brazil, given the lack of horse antithymocyte globulin in many markets outside the United States.

☆ Please cite this article as: Garanito MP, Carneiro JD, Odone Filho V, Scheinberg P. Outcome of children with severe acquired aplastic anemia treated with rabbit antithymocyte globulin and cyclosporine A. J Pediatr (Rio J). 2014;90:523–7.
☆☆ Study conducted at Serviço de Oncologia e Hematologia of Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
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http://dx.doi.org/10.1016/j.jped.2014.02.004

PALAVRAS-CHAVE
Anemia aplástica;
Terapia imunossupressora;
Globulina antitimocítica;
Pancitopenia;
Recorrência;
Evolução clonal

Resultado de crianças com anemia aplástica grave adquirida tratadas com globulina antitimocítica de coelho e ciclosporina A

Resumo

Objetivo: Avaliar o resultado de crianças com anemia aplástica grave adquirida tratadas com globulina antitimocítica de coelho e ciclosporina como tratamento inicial em nosso instituto.
Métodos: Análise retrospectiva de 26 pacientes pediátricos com anemia aplástica tratados entre 1996 e 2011 com globulina antitimocítica de coelho e ciclosporina.
Resultados: A taxa de resposta geral em seis meses foi de 34,6% (9/26), e a incidência acumulada de recorrência foi de 26,5% (intervalo de confiança [IC] de 95%,1,4%-66%) em cinco anos. A incidência acumulada de evolução clonal após a terapia imunossupressora foi de 8,3% (IC 95%, 0,001%-53,7%) em cinco anos, com ambas as evoluções clonais em pacientes sem resposta que adquiriram o cariótipo com monossomia 7. A sobrevida geral em cinco anos foi de 73,6% (IC 95%, 49,2%-87,5%).
Conclusões: Nossos resultados confirmam a baixa taxa de resposta com globulina antitimocítica de coelho como terapia inicial em pacientes pediátricos, da mesma forma como relatado para pacientes de todas as idades. Essa confirmação é problemática em nosso país devido à falta de globulina antitimocítica de cavalo em muitos mercados fora dos Estados Unidos, incluindo o Brasil.

Introduction

Severe aplastic anemia (SAA) is a rare hematological disease characterized by pancytopenia and a hypocellular bone marrow. In SAA, cellular marrow elements are replaced by fat as a result of an immune-mediated destruction of stem and progenitor cells.[1] Until recently, it was believed that fat replacement was a benign process; however, recent data suggest that it might be a negative regulator of hematopoiesis, contributing to marrow failure.[2] Hematopoiesis can be restored in SAA following hematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy (IST). In children and young adults, HSCT is preferred when a histocompatible sibling donor is available; for all other patients, IST is often employed as first therapy.[3–5] The standard IST is with a combination of horse antithymocyte globulin (ATG) and cyclosporine (CsA).[6] More potent lymphocytotoxic agents, such as rabbit ATG, alemtuzumab, and cyclophosphamide, have yielded disappointing results in treatment-naïve SAA due to lack of efficacy and/or increased toxicity.[7–10] Response rates to horse ATG/CsA have been consistent across studies in the US, Europe, and Japan, and have varied between 60% and 75%.[1,4,11–13] In general, children have a higher hematologic response rate in the 70% to 80% range, while older adults (> 40-50 years of age) have reported response rates in the 50% to 60% range.[14–17]

Rabbit ATG is manufactured similarly to horse ATG, but has greater lymphocytotoxic properties on a weight basis.[18,19] Human T-cells derived from a thymus or T-cell line is used to sensitize an animal, whether horse or rabbit, which will produce polyclonal antibodies with a multitude of specificities to molecules expressed in human T cells. This polyclonal sera is then purified for administration in humans. Rabbit ATG has been successful in salvaging SAA patients after initial horse ATG failure and in kidney allograft, and was shown to be superior to horse ATG in head-to-head comparison.[20–22] However, when given as first therapy, outcomes with rabbit ATG were inferior to horse ATG in a randomized study.[8] Follow-up retrospective reports have confirmed a lower response rate in patients treated with rabbit ATG as first therapy when compared to horse ATG.[23–26] However, the majority of the reports have not focused on children. This article aimed to report the results in pediatric patients who received rabbit ATG as first therapy for SAA treated at the Instituto da Criança of the Universidade de São Paulo, São Paulo, Brazil.

Patients and Methods

Patients

This study included consecutive patients with SAA who received rabbit ATG/CsA between August of 1996 and of June 2011 at the Instituto da Criança of the Universidade de São Paulo. Due to the unavailability of the horse ATG in this service and in Brazil since 2007, rabbit ATG became the standard immunosuppressor in SAA patients without an HLA-identical sibling donor. All patients met the criteria for SAA, defined as a bone marrow cellularity of less than 30% and severe pancytopenia with at least two of the following peripheral blood count criteria: (1) absolute neutrophil count (ANC) < 0,5 x 10^9/lL (2) absolute reticulocyte count (ARC) < 60x10^9/L; platelet count < 20x10^9/L.[27] Exclusion criteria were: (1) abnormal cytogenetics, (2) bone marrow morphology consistent with myelodysplasia, and (3) diagnosis of Fanconi anemia. Bone marrow biopsy and aspirate, including cytogenetics, were performed before initiating therapy. Fanconi anemia was excluded by the absence of chromosomal changes after exposure *in vitro* of lymphocytes