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Research paper

Comparative study of porcine anti-human lymphocyte immunoglobulin and rabbit anti-human thymocyte immunoglobulin as a first-line treatment of acquired severe aplastic anemia

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ABSTRACT

Porcine anti-human lymphocyte immunoglobulin (pALG) and rabbit anti-human thymocyte immunoglobulin (rATG) are the only two ATGs for severe aplastic anemia (SAA) treatment in China. 148 treatment-naïve SAA patients who received ATG combined with cyclosporine A (CsA) therapy were analysed retrospectively. The patients were divided into a pALG group (n = 114) and a rATG group (n = 34). After three months, the pALG and rATG groups had an overall response (OR) of 65.8% and 44.1%, respectively (P = 0.023); after six months, the OR reached 74.6% and 64.7%, respectively (P = 0.361). The pALG group had markedly better time-related efficacy than the rATG group (P = 0.03). The overall survival (OS) and event-free survival (EFS) between groups had no significant difference (P > 0.1). The pALG and rATG groups did not significantly differ in terms of recurrence (8.8% vs. 5.9%, P = 0.734) or PNH clonal transformation (5.3% vs. 2.9%, P = 1.000), whereas a significant difference was found in the incidence of MDS/AML transformation (2.6% vs. 11.8%, P = 0.049). We found that pALG achieved a better time-related efficacy than rATG for the treatment of SAA; nonetheless, no significant difference in the OS or EFS of pALG compared with rATG.

1. Introduction

Acquired aplastic anemia (AA) is a bone marrow failure disease mainly due to T lymphocyte-mediated immune destruction of hematopoietic stem cells (HSCs), and it primarily manifests as pancytopenia and infection [1]. Immunosuppressive therapy (IST) is the first-line treatment of patients who are unsuitable for allogeneic HSC transplantation. The combined use of anti-human thymocyte immunoglobulin (ATG) and cyclosporine A (CsA) is now recognized as the standard intensive IST [2], which markedly improves the prognosis of patients with severe AA (SAA).

ATG is obtained by immunizing animals with cells from foetal or neonatal thymic tissues. Owing to the different species of immunized animals, ATG currently encompasses horse ATG (hATG), rabbit ATG (rATG) and porcine ATG (pALG), among various other types. The combination of hATG with CsA as a first-line treatment of SAA achieves a hematological response of 60–75% [3], while rATG as a second-line treatment achieves an overall response (OR) of 30–77% in patients who are non-responsive to hATG or who have recurrence after hATG therapy [4,5]. Several comparative studies, including prospective studies of hATG and rATG as first-line treatments for SAA showed that the therapeutic efficacy and survival are worse for rATG than for hATG [6–8], although rATG is generally thought to have a stronger immunosuppressive effect than hATG.

Currently, hATG is unavailable in the Chinese market. Since the 1980s, pALG, a formulation made in China, has been used to treat Chinese patients with SAA. The State Food and Drug Administration of China approved pALG for marketing in 2004, and pALG has been increasingly used widely; the efficacy of pALG is reported to reach 74.5–83.3% [9–11]. To date, only two retrospective comparative studies of rATG and pALG have been reported [12,13], and they suggested that the efficacy and survival of pALG are similar or superior to those of rATG when used as a first-line treatment of SAA. More abundant and sufficient data may change the suggested options for first-line drugs for intensive IST treatment of SAA in China.

Here, we report a retrospective study of pALG and rATG for the treatment of SAA. Ordinal logistic regression and COX regression analyses were conducted to compare the efficacy and survival between two groups of patients. Propensity score weighting was used to eliminate the non-randomness of the retrospective samples and control the potential influence of confounding variables on the efficacy assessment model. This study will provide more sufficient information for the

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option of first-line treatment regimen for SAA patients in China.

2. Subjects and methods

2.1. Ethics statement

All procedures followed were in accordance with the ethical standards of the Ethics Committee of Peking Union Medical College Hospital and with the Helsinki Declaration of 1975, as revised in 2008. Patient information was anonymized and de-identified prior to analysis.

2.2. Subjects

A retrospective analysis was conducted on 148 treatment-naïve SAA patients (age > 12 years old) who were hospitalized at Peking Union Medical College Hospital and treated using pALG/rATG combined with CsA therapy from 1996 to 2015. The patients included 114 individuals who received pALG combined with CsA therapy (pALG group) and 34 who received rATG combined with CsA therapy (rATG group). AA diagnosis and severity determination were performed based on the diagnostic criteria defined by Camitta et al. [14,15], with congenital AA being excluded. The paroxysmal nocturnal hemoglobinuria (PNH) clone was defined as a positive acid hemolysis test or Ham's test (before 2007) or as neutrophils with CD59-negative cells ≥ 5% (from 2007 to 2010) or FLEAR-negative cells ≥ 1% (after 2010) along with the development of flow cytometry in our laboratory. Hemolytic PNH was defined as the presence of a significant PNH clone associated with clinical or laboratory evidence of hemolysis [2]. The presence of various infections, fever without a clear infection focus, brain hemorrhage, hepatic dysfunction (> 2 times the upper normal limit) and renal dysfunction at one week before intensive IST treatment was defined as a comorbidity during intensive IST treatment.

2.3. Methods

All patients underwent intensive IST treatment (pALG/rATG plus CsA) from 1996 to 2015, with no IST or only CsA therapy before enrollment. Allogeneic HSC transplantation was not possible due to the donor shortage or economic reasons. The subjects' data were collected from January 2013 to June 2016 and were analysed form June 2016 to September 2016. The treatment regimen was as follows: (1) pALG (Wuhan Institute of Biological Products Co., Ltd., Wuhan, Hubei, China): 20–30 mg/kg/day, for five days; rATG (Genzyme Polyclonals S.A.S, Lyon, France): 3–5 mg/kg/day, for five days; methylprednisolone 1 mg/kg/day was administered with dose tapering over one month to prevent serum sickness; (2) CsA: 3–5 mg/kg/day, with the blood trough concentration being monitored and maintained at ~200 ng/ml; the dose was gradually decreased after response, and the treatment was continued for more than two years; (3) adjuvant therapy: hematopoietic growth factors, such as granulocyte colony-stimulating factor, blood component transfusion and anti-infection therapy; and (4) antifungal prophylaxis for particular patients as determined by the physician, with fluconazole, itraconazole or posaconazole. Patients were re-examined after three, six and twelve months of IST treatment. We assessed the patients' clinical manifestations and re-examined their whole blood cells and reticulocytes, hepatic and renal function, CsA concentration and CD55 and CD59 on peripheral red blood cells and neutrophils. Bone marrow smears and biopsies were re-examined according to clinical indications. Thereafter, the assessment was carried out every 3–6 months. Nonresponsive patients were treated with a second course of intensive IST, or with traditional Chinese medicine or blood transfusion as supportive care. Recurrent patients were treated with a second course of intensive IST or with CsA only. Patients with transplantation as a rescue therapy were excluded in both groups.

2.4. Efficacy criteria

Efficacy was assessed according to the standards published by Marsh J.C.W. in 2009 [16] : (1) Complete response (CR): absolute neutrophil count > 1.5×10^9/L, hemoglobin > 110 g/L, platelet > 100×10^9/L; (2) Partial response (PR): no longer meeting criteria for SAA and not dependent on red blood cell or platelet transfusions; (3) Non-response (NR): continuous transfusion dependence after treatment without complete blood count improvement; (4) Recurrence: peripheral blood cell count reductions to SAA levels after CR or PR, regardless of transfusion dependence. When assessing the efficacy, hematopoietic growth factors were withdrawn for more than two weeks, and routine blood test parameters were maintained at stable levels for up to four weeks.

We defined complete response (CR) and partial response (PR) as "response", and non- response (NR) and death as "nonresponse". The speed of response is also an important feature that reflects medicinal properties and efficacy. Therefore, to evaluate the effect of time on efficacy, we used "response or not" and "time to response" to comprehensively assess the efficacy of intensive IST treatment. Therefore, a new efficacy variable was defined and assigned to be 0, 1 or 2. Specifically, 0 indicates "nonresponse" at both three and six months; 1 indicates "nonresponse" at three months but "response" at six months; and 2 indicates "response" at both three and six months. Thus, the outcome "2" indicates not only that a patient had a response but also that his/her response was rapid.

2.5. Statistical analysis

Data were statistically analysed using two statistical software packages, SPSS 20.0 (IBM SPSS, Somers, NY, USA) and R 3.3.1 (R Development Core Team, 2008). Two constituent ratios were compared using a contingency table chi-squared test, and data cells with an expected count less than five were analysed by Fisher's exact test. Measurement data with a normal distribution and equal variances were compared using the independent samples *t*-test, and measurement data that failed to show a normal distribution were compared using the Wilcoxon rank sum test. The Kolmogorov-Smirnov (K-S) statistic was used to test whether there was a significant difference in the distribution. An ordinal logistic regression model was adopted to compare the efficacy between two treatment groups. Survival analysis was conducted using the weighted Kaplan-Meier method, and the survival was compared using the weighted log-rank test. COX regression analysis was conducted to examine the difference in the survival between the two treatment groups. We also applied propensity score weighting to the above models to eliminate the non-randomness of retrospective data. Overall survival (OS) means the time from entry to any cause of death. And the time of last follow-up of the lost patients was analysed as the time of death. Event free survival (EFS) is the time from entry to any events including death, loss to follow-up, recurrence and clonal transformation (myelodysplastic syndrome, leukemia and paroxysmal nocturnal hemoglobinuria). A difference was considered statistically significant at $P < 0.05$.

3. Results

3.1. Patient characteristics

Table 1 shows the clinical characteristics of the patients in the pALG group (n = 114) and the rATG group (n = 34). The median age of pALG and rATG group was 30(12–72) and 35.5(14–76) respectively. Compared with the rATG group, the pALG group had a significantly higher pre-treatment absolute neutrophil (NEUT) count. No significant difference was found in the remaining characteristics shown in Table 1.