Leukemia Research 39 (2015) 284–289

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Early intensified intravenous cyclosporine therapy predicts favorable response to immunosuppressive therapy with rabbit antithymocyte globulin in patients with severe aplastic anemia

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ARTICLE INFO

Article history:
Received 5 November 2014
Received in revised form
10 December 2014
Accepted 16 December 2014
Available online 24 December 2014

Keywords:
Aplastic anemia
Antithymocyte globulin
Cyclosporine

ABSTRACT

Because of relapse after horse ATG (hATG) therapy, rabbit ATG (rATG) would be a realistic alternative as second line immunosuppressive therapy (IST) in severe aplastic anemia (SAA) patients. We investigated whether intensified intravenous (IV) CsA therapy with rATG would increase the response of IST in SAA patients.

Sixty-one of the 123 patients received IV CsA therapy with rATG during initial 2 weeks then changed to oral form (IV CsA group), while other 62 patients just received oral CsA therapy with rATG (oral CsA group).

Hematologic response rates at 3 and 6 months were not different between IV CsA group and oral CsA group ($p = 0.795$, $p = 0.079$). However, CsA levels during initial 15 days were higher in response-achieved group than response-not-achieved group. Intensive IV CsA group maintained CsA level ≥300 ng/ml during 15 days had higher responses at 6 months than non-intensive IV CsA group and oral CsA group ($p = 0.009$, $p = 0.021$). Intensive IV CsA group (HR = 3.239, 95% CI = 1.095–8.997, $p = 0.013$) independently predicted favorable the hematologic response at 6 months of IST.

Early intensified CsA therapy was important to achieve favorable outcomes in IST including rATG.
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1. Introduction

Severe aplastic anemia (SAA) is a life-threatening disease, characterized by pancytopenia and bone marrow hypocellularity [1]. T-cell mediated destruction of hematopoietic progenitors and stem cells is pathogenic in most of the cases. In several large prospective trials, the efficacy of immunosuppressive therapy (IST) including horse antithymocyte globulin (hATG) in SAA patients ineligible for bone marrow transplantation (BMT) was well established [2–5]. Hematologic response to IST with hATG is achieved in about 60–80% of the cases and this group showed excellent long-term clinical outcomes. On the other hand, rabbit ATG (rATG) has been used as second-line treatment for relapsed patients or non-responders to IST with hATG [6,7]. Additionally, other clinical studies which investigated the clinical impact of rATG as first-line IST in SAA patients showed inferior results compared with those in studies using hATG [8,9].

Because of the restricted availability of hATG in some countries, rATG is used as first-line IST in SAA patients ineligible for BMT. Moreover, the two ATGs have significantly different mechanisms of action, although they share some common properties. Therefore, after gaining an understanding of the differences in characteristics of rATG and hATG, it would be necessary to have a novel therapeutic option to improve the response to IST with rATG in SAA patients ineligible for BMT.

Addition of cyclosporine A (CsA) to ATG improved the overall response rate, and therefore, this regimen is the current standard protocol for immune suppression in SAA patients [2,10–12]. CsA is a calcineurin inhibitor that impairs interleukin (IL)-2-dependent T cell activation and differentiation. Therefore, intensive

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http://dx.doi.org/10.1016/j.leukres.2014.12.011
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immunosuppression with CsA would suppress pathogenic T cell clones which were not fully eliminated by rATG in IST, and would increase the hematologic response and survival.

In the present study, we investigated whether intensive therapeutic strategy using intravenous (IV) CsA combined with rATG would be more effective than ordinary IST including oral CsA combined with rATG as the control group in SAA patients ineligible for BMT, retrospectively.

2. Patients and methods

One hundred twenty-three patients with acquired severe and very severe aplastic anemia (VSAA) who were initially diagnosed from 2002 to 2012 and who received rATG (thymoglobulin) combined with intravenous or oral CsA, were enrolled in this study. SAA and VSAA were defined according to the standard criteria [13].

The participating patients from 4 medical centers (Pusan National University Hospital, Busan Haeundae Paik Hospital, Gyeong-Sang National University Hospital, and Gachon University Gil Medical Center) were ineligible for HLA-identical sibling donor BMT, and had not received prior IST with any ATG or CsA. Approval for reviewing the patient records was obtained from each Institutional Review Board.

The patients were excluded if they were eligible for BMT, had received prior IST with ATG or CsA, had received hematopoietic growth factor more than 4 weeks before enrollment in our study, showed evidence of Fanconi anemia, dyskeratosis congenita, or congential bone marrow failure syndrome, showed evidence of myelodysplastic syndrome, or had uncontrolled infection.

2.1. Treatment schedule

The dose of rATG was 3.5 mg/kg daily for 5 days, given as an IV infusion over 12–18 h. The starting dose of CsA was 5 mg/kg per day as a continuous IV infusion from day 2. Trough levels <200 ng/ml or >400 ng/ml on day 1 were adjusted by increasing or decreasing the CsA dose by at least 25%. To evaluate whether intensive IV CsA during the early stage of IST would be effective in patients with SAA, the trough whole blood CsA levels were adjusted daily to maintain the target level between 200 and 400 ng/ml from seven to eight in the morning during the initial 2 weeks after IST. Then, IV CsA was changed to an oral agent after the second week, and then oral CsA was given for a minimum period of 6 months. To prevent serum sickness, methylprednisolone (or prednisone) 2 mg/kg per day was given from days 1 to 5, then tapered to half-dose every 3 days. An anti-histamine was given before each ATG infusion. Prophylactic antifungal, antibacterial, and antiviral agents were given. The patient group that received the treatment schedule was classified as the IV CsA group. Response was estimated according to the established criteria [13]. To evaluate the clinical efficacy of IV CsA, the patients who received rATG combined with only oral CsA from day 1 to a minimum period of 6 months were included as the control group. This patient group was classified as the oral CsA group.

2.2. Statistical analysis

Mann–Whitney *U*-test was used to compare differences in clinical features between the separate subgroups. Comparisons of trough CsA levels according to the response were made by Student's *t*-test. The cumulative incidence of response was compared using the log-rank test. Overall survival (OS) was calculated from the initial date of IST until death due to any cause or the last date the patient was known to be alive using the Kaplan–Meier method. Cox proportional hazard model was used to analyze various prognostic factors for PFS and OS in the univariate and multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined for all survival endpoints. The statistical analysis was carried out with SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Table 1
The baseline characteristics of the patients with SAA.

	Total	IV CsA group	Oral CsA group	p-value
Number	123	61 (49.6)	62 (50.4)	
Median age at diagnosis (range), years	51 (21–77)	51 (26–76)	54 (28–77)	0.280
≥50 years	65 (52.8)	33 (26.8)	32 (26.0)	0.783
<50 years	58 (47.2)	28 (22.8)	30 (24.4)	
Sex (%)				0.645
Male	68 (55.3)	35 (28.5)	33 (26.8)	
Female	55 (44.7)	26 (21.1)	29 (23.6)	
Severity of AA (%)				0.968
SAA	103 (83.8)	51 (41.5)	52 (42.3)	
VSAA	20 (16.2)	10 (8.1)	10 (8.1)	
PNH clone (%)				0.559
Presence	29 (23.6)	13 (10.6)	16 (13.0)	
Absence	94 (76.4)	48 (39.0)	46 (37.4)	
Transfusion before IST				
RBC transfusion (range), units	12 (2–28)	6 (2–28)	6 (2–26)	0.172
PLT transfusion (range), units	18 (6–88)	22 (6–88)	18 (2–82)	0.129
Interval from diagnosis to IST				
Median interval (range), months	3.5 (0.4–36.2)	3.6 (0.4–36.0)	3.5 (0.5–36.2)	0.205
≥3 months (%)	39 (31.8)	19 (15.5)	20 (16.3)	0.197
<3 months (%)	84 (68.2)	42 (34.1)	42 (34.1)	
Median, WBC count (range), $\times 10^9$/L	1.45 (0.26–3.40)	1.78 (0.26–3.06)	1.31 (0.35–3.40)	0.070
Median, ANC, (range), $\times 10^9$/L	0.36 (0.10–0.93)	0.40 (0.10–0.91)	0.35 (0.12–0.93)	0.098
Median, ARC, (range), $\times 10^9$/L	18.1 (1.1–72.3)	18.1 (1.1–54.2)	17.3 (1.5–72.3)	0.508
Median, ALC, (range), $\times 10^9$/L	0.47 (0.11–1.81)	0.47 (0.11–1.80)	0.45 (0.12–0.97)	0.702
Median, PLT count (range), $\times 10^9$/L	16 (2–42)	15 (2–32)	17 (7–42)	0.193

SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; IST, immunosuppressive therapy; RBC, red blood cell; PLT, platelet; WBC, white blood cell; ANC, absolute neutrophil count; ARC, absolute reticulocyte count; ALC, absolute lymphocyte count.

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