Original article

Clinical outcomes of pediatric patients with severe idiopathic aplastic anemia in King Chulalongkorn Memorial Hospital

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Abstract:

Background: *Idiopathic severe aplastic anemia (SAA) is a rare disorder among children. The modality of treatment is matched sibling, allogeneic stem cell transplantation or immunosuppressive among patients who do not have a matched donor as first line therapy. The responses to the treatment vary depending on the reports.* ***Objecti ves:*** *The study aimed to evaluate the outcomes of children with idiopathic SAA in our institution.* ***Methods:*** *A retrospective chart review included all patients aged 1 to 18 years, diagnosed with SAA between June 1, 2004 and June 30, 2019, who had been treated at King Chulalongkorn Memorial Hospital.* ***Results:*** *Thirty pediatric patients (22 males and eight females) median age 6.4 years were enrolled. Twenty-three patients (76%) received ATG plus cyclosporine, while 3 patients (10%) received androgen plus low dose prednisolone as a first treatment. Eight patients, (34.7%) receiving ATG plus cyclosporine, achieved a response at 3 months. Among unresponsive patients, 8 patients (53.3%) received androgen plus low dose prednisolone while the remaining 7 patients received 2nd ATG plus cyclosporine. Five-year overall survival was 72.9% (95%CI: 0.49 – 0.86) in the ATG plus cyclosporine group. Four patients underwent matched sibling, allogeneic stem cell transplantation while 3 patients survived without the disease. The 5-year overall survival of all patients was 69.4% (95%CI: 0.49 – 0.82), and the median follow-up totaled 4.3 years.* ***Conclusion:*** *This study demonstrated that treatment of SAA using immunosuppressive therapy, consisting of ATG plus cyclosporine, had acceptable outcomes. Matched sibling, allogeneic stem cell transplantation is considered a first-line treatment with superior outcomes compared with immunosuppressive therapy. However, the limitation is donor availability.*

Keywords : ● *Severe aplastic anemia* ● *Immunosuppressive therapy* ● *Stem cell transplantation*

J Hematol Transfus Med. 2020;30:263-70.

Received 7 May 2020 Corrected 11 May 2020 Accepted 30 July 2020

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นิพนธ์ต้นฉบับ

การศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค severe idiopathic aplastic anemia ในโรงพยาบาลจุฬาลงกรณ์

อรพรรณ คัดทะจันทร์ หรรษมน โพธิ์ผ่าน สุภานัน เลาหสุรโยธิน ปิติ เตชะวิจิตร์ ดารินทร์ ซอโสตถิกุล และ ปัญญา เสกสรรค์
สาขาวิชาโลหิตวิทยาและมะเร็งในเด็ก ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

บทนำ *โรคไขกระดูกฝ่อชนิดรุนแรงพบได้น้อยในผู้ป่วยเด็ก โดยพบปริมาณเม็ดเลือดทุกชนิดต่ำกว่าปกติและไขกระดูกทำงานลดลง การรักษาทำได้โดยการปลูกถ่ายไขกระดูกในผู้ป่วยที่มีพี่น้องที่มีความเข้ากันได้ของเนื้อเยื่อ แต่ในปัจจุบันการรักษาหลักส่วนใหญ่เป็นการใช้ยากดภูมิคุ้มกันซึ่งผลการรักษามีความแตกต่างกันในผู้ป่วยเด็ก* ***วัตถุประสงค์*** *เพื่อศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค Idiopathic Severe aplastic anemia ในโรงพยาบาลจุฬาลงกรณ์* ***รูปแบบการวิจัย*** *การศึกษาย้อนหลังเชิงพรรณนา โดยการทบทวนเวชระเบียนผู้ป่วยที่วินิจฉัยด้วย Idiopathic severe aplastic anemia ที่รักษาในโรงพยาบาลจุฬาลงกรณ์ ในช่วงระหว่างวันที่ 1 มิถุนายน 2547 ถึง 30 มิถุนายน 2562* ***ผลการวิจัย*** *ผู้ป่วยทั้งหมด 30 คน(เพศชาย 22 คน, เพศหญิง 8 คน) อายุเฉลี่ยแรกวินิจฉัย 6.4 ปี (1-14 ปี) ผู้ป่วยจำนวน 23 คน (76%) ได้รับการรักษาโดย ATG ร่วมกับ cyclosporine ผู้ป่วยจำนวน 3 คน ได้รับการรักษาโดย androgen ร่วมกับ prednisolone ขนาดต่ำ ผู้ป่วย 4 รายได้รับการปลูกถ่ายไขกระดูก ผลการรักษาพบว่าผู้ป่วยในกลุ่มที่ได้รับการรักษาโดย ATG ร่วมกับ cyclosporine จำนวน 8 คน (34.7%) ตอบสนองต่อการรักษาใน 3 เดือนแรกหลังได้รับยา ผู้ป่วยจำนวน 15 คนต้องได้รับการรักษาเพิ่มเติมหลังจากการรักษาครั้งแรกและมีการตอบสนองต่อการรักษาเฉลี่ย 6.9 เดือน (1-21 เดือน) ผู้ป่วยจำนวน 3 คนในกลุ่มที่ได้รับการปลูกถ่ายไขกระดูกมีชีวิตโดยปราศจากโรค อัตราการรอดชีวิตที่เวลา 5 ปีของผู้ป่วยทั้งหมดร้อยละ 69.4 (95%CI: 0.49-0.82) ระยะเวลาเฉลี่ยที่ผู้ป่วยมาติดตามการรักษา 4.3 ปี* ***สรุป*** *จากผลการศึกษานี้แสดงให้เห็นว่าในปัจจุบันแนวทางการรักษาในผู้ป่วย Idiopathic severe aplastic anemia ยังคงเป็นการใช้ยากดภูมิคุ้มกันเป็นหลัก ซึ่งผลการรักษาเป็นที่น่าพอใจ ผู้ป่วยที่ได้รับการปลูกถ่ายไขกระดูกมีผลการรักษาที่ดีกว่าแต่มีข้อจำกัดหากไม่มีพี่น้องหรือไม่มีผู้บริจาคที่เข้ากันได้*

คำสำคัญ : ● *ภาวะไขกระดูกฝ่อรุนแรง* ● *การใช้ยากดภูมิคุ้มกัน* ● *การปลูกถ่ายไขกระดูก*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:263-70.

Introduction

Severe aplastic anemia[1,2] is a rare pediatric hematological disorder characterized by peripheral cytopenia and hypocellular bone marrow. Approximately 70 to 80% of patients are categorized as idiopathic because their primary etiology is unknown.[2,3] Twenty percent of children with severe aplastic anemia is caused by infection, medications, chemical substances or inherited disorders. Patients with severe aplastic anemia commonly present anemia, abnormal bleeding and fever with no clinical of organomegaly. The diagnosis of severe aplastic anemia includes at least two of the following laboratory criteria: 1) Hemoglobin less than 8 g/dL, 2) absolute neutrophil count (ANC) less than 500/uL and 3) platelet count less than 20,000/uL with evidence of bone marrow hypocellularity or cellularity less than 25% by pathological study.[4]

The standard first-line treatment for newly diagnosed severe aplastic anemia is allogeneic stem cell transplantation from an HLA-sibling donor with a reported 70 to 80% 5-year survival rate among children. Immunosuppressive therapy combining ATG and cyclosporine is considered first-line treatment among patients without HLA-matched sibling donors.[1] Treatment response with ATG plus cyclosporine in the US, Europe and Japan has been reported from 60 to 75%.[5] However, the result of the treatment outcomes among pediatric patients in Thailand has not been reported.

Objective

The study aimed to evaluate the outcomes of children with severe idiopathic aplastic anemia treated with anti-thymoglobulin plus cyclosporin, androgen plus low dose prednisolone and matched sibling allogeneic stem cells transplantation in our institution.

Methods

A retrospective chart review of all patients aged 1 to 18 years with a diagnosis of severe aplastic anemia between June 1, 2004 and June 30, 2019 were treated and followed-up at King Chulalongkorn Memorial Hospital. This study was approved by the Institutional Review Board (IRB) in our institution. All patients met the criteria of severe aplastic anemia. The definition included bone marrow cellularity less than 25% and severe pancytopenia with at least two of the peripheral blood count criteria: absolute neutrophil count ≤ 500 /uL, platelets count ≤ 20,000 /uL and anemia with corrected reticulocyte count ≤ 1%. Exclusion criteria included equivocal diagnosis of aplastic anemia, bone marrow failure from other causes and inherited bone marrow failure syndrome. Bone marrow aspiration and biopsy were performed before initiating therapy. All patients were hospitalized to administer rabbit ATG at dose 5 mg/kg/day totally 5 days. Serum sickness prophylaxis with methylprednisolone 2 mg/kg/day before ATG administration was continued tapered over 10 to 14 days. Cyclosporine was initiated day 6 at 8 to 10 mg/kg/day adjusted to therapeutic levels (150-250 ng/mL). The data included demographics, clinical presentation at diagnosis, treatment modalities, outcomes of each treatment at 3, 6, 12 and 24 months and complications of disease and treatments. The outcomes of treatment response were defined by: Hb ≥ 8 g/dL, ANC ≥ 500 /uL and platelet ≥ 20,000 /uL. Statistical analyses were used in the study including frequency, median and Kaplan-Meier method in overall survival.

Results

A total of 30 pediatric patients received a diagnosis of severe idiopathic aplastic anemia between June 1, 2004 and June 30, 2019. They received immunosuppressive therapy including ATG dose 5 mg/kg/day for five consecutive days plus cyclosporine 10 mg/kg/day (adjusted to therapeutic blood levels 150 to 250 ng/mL) or androgen plus low dose prednisolone and allogeneic stem cells transplantation in our institution. Demographic data (Table 1) shows that 73.3% of patients (22/30) were male, all patients previously healthy and age at diagnosis range 1 to 14 years (median 6.4 years). Four patients had matched sibling donors. The median (range) follow-up time was 4.3 (0.5-16) years.

Table 1 Baseline demographic data, clinical features and laboratory testing at diagnosis

	Number (N)	Percentage (%)
Total subjects (N)	30	100
Sex		
Male	22	73.3
Female	8	26.7
Race		
Thai	29	96.7
NonThai	1	3.3
Age (years)		
0-5	14	46.7
> 5-10	10	33.3
> 10-15	6	20
Underlying disease		
No underlying disease	29	96.7
Specific underlying disease	1	3.3
Sibling		
Matched sibling	4	13.3
No matched sibling	11	36.7
No sibling	14	50
Clinical		
Anemia	30	100
Abnormal bleeding	27	90
Fever	16	53.3
Hepatomegaly	0	0
Splenomegaly	0	0
Laboratory testing		
● Complete blood count (CBC)		
Pancytopenia	23	76.7
Bicytopenia	7	23.3
● Initial ANC		
< 200	7	23.3
200-500	9	30
501-1,500	9	30
> 1,500	5	16.7

Table 1 Baseline demographic data, clinical features and laboratory testing at diagnosis (continued)

	Number (N)	**Percentage (%)**
Laboratory testing		
● Chromosome		
Done	14	46.7
- Normal	13	92.8
- no metaphase	1	7.2
Not done	16	53.3
● PNH clone		
Done	7	20
- Detected	0	0
- Undetected	7	100
Not done	23	80
Infectious work up		
● Viral hepatitis		
Not done	9	30
Done	21	70
- Positive	0	0
- Negative	21	100
● CMV		
Not done	11	36.7
Done	19	63.3
- Positive	19	100
- Negative	0	0
● EBV		
Not done	11	36.7
Done	19	63.3
- Positive	18	94.7
- Negative	1	5.3
● Parvovirus		
Not done	16	53.3
Done	14	46.7
- Positive	14	100
- Negative	0	0

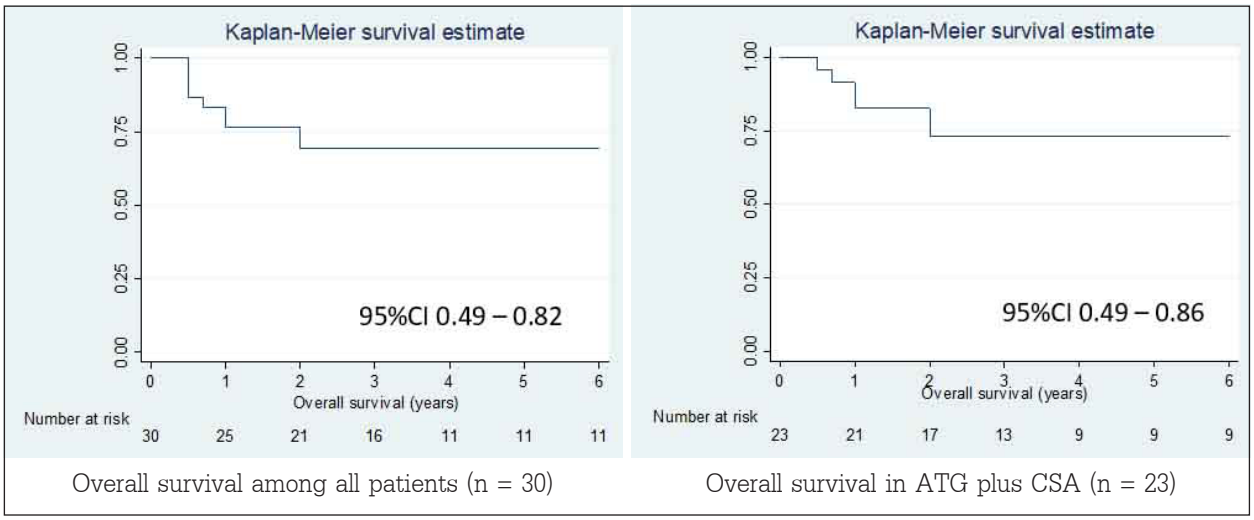
Almost all patients presented anemia, 27 patients (90%) with abnormal bleeding and 16 patients (53.3%) with fever. Complete blood count results among 23 patients (76.7%) indicated pancytopenia while the rest were bicytopenia. One half of the patients had absolute neutrophil count (ANC) less than 500/uL while one fourth had ANC less than 200/uL. Five patients had absolute neutrophil count (ANC) more than 1,500/uL at initial diagnosis but met the other peripheral blood count criteria and bone marrow cellularity ≤ 25%. Bone marrow chromosome testing was performed in 46.7% of patients and 92.8% reported normal chromosome. PNH clone test by flow cytometry was performed in 20% of all patients and all reported negative. The infectious workups including viral hepatitis (21 patients), CMV (19 patients) parvovirus (14 patients) and EBV (28 patients) were investigated as shown in Table 1. Only one patient was positive for EBV.

The treatment is summarized in detail below. Twenty-three patients (76.7%) received rabbit ATG plus cyclosporine, four patients (13.3%) underwent matched sibling allogeneic stem cell transplantation and three patients (10%) received androgen plus low dose prednisolone.

Treatment response was defined by Hb ≥ 8 g/dL, ANC ≥ 500/uL and platelet ≥ 20,000/uL and assessed at 3, 6, 12 and 24 months after treatment. The overall responses were 40, 43.3, 50 and 63.3% at 3, 6, 12 and 24 months, respectively. Treatment responses were sub-classified as completed response (Hb ≥ 10 g/dL, ANC ≥ 1,000/uL, platelet ≥ 100,000/uL), very good partial response (Hb ≥ 8 g/dL, ANC ≥ 500/uL, platelet ≥ 50,000/uL) and partial response (Hb ≥ 8 g/dL, ANC ≥ 500/uL, platelet ≥ 20,000/uL). Responses less than partial response were classified as nonresponse. Table 2 shows summarized treatment responses among all patients.

Table 2 Response to treatment

N = 30	3 months	6 months	12 months	24 months
● All patients (n = 30)				
- Complete response	2(6.7%)	7(23.3%)	7(23.3%)	12(40%)
- Very good partial response	7(23.3%)	3(10.0%)	5(16.7%)	2(6.7%)
- Partial response	3(10.0%)	3(10.0%)	3(10.0%)	5(16.7%)
- No response	18(60.0%)	17(56.7%)	15(50.0%)	11(36.7%)
● ATG plus cyclosporine (n = 23)				
- Complete response	0(0%)	4(17.4%)	5(21.7%)	8(34.8%)
- Very good partial response	6(26%)	3(13%)	4(17.4%)	2(8.7%)
- Partial response	2(8.7%)	2(8.7%)	2(8.7%)	5(21.8%)
- No response	15(65.3%)	14(60.9%)	12(52.2%)	8(34.7%)
● Allogeneic HSCT (n = 4)				
- Complete response	2(50%)	3(75%)	3(75%)	3(75%)
- Very good partial response	1(25%)	0(0%)	0(0%)	0(0%)
- Partial response	0(0%)	0(0%)	0(0%)	0(0%)
- No response	1(0%)	1(0%)	1(0%)	1(0%)
● Androgen (n = 3)				
- Complete response	0(0%)	0(0%)	0(0%)	0(0%)
- Very good partial response	0(0%)	0(0%)	2(66.7%)	2(66.7%)
- Partial response	2(66.7%)	2(66.7%)	0(0%)	0(0%)
- No response	1(33.3%)	1(33.3%)	1(33.3%)	1(33.3%)



Overall survival among all patients (n = 30) | Overall survival in ATG plus CSA (n = 23)

Figure 1 Overall survival among patients with severe aplastic anemia

Three quarters of all patients received ATG plus cyclosporine as a first treatment modality. The result showed response to treatment in this group of 34.7, 39.1, 47.8 and 65.3% at 3, 6, 12 and 24 months. None of the patients treated with ATG achieved a complete response in the first three months after treatment but subsequently achieved complete response 17.4% at six months and 34.8% at 24 months (Table 2). One half of all patients received subsequent treatment. The most common subsequent treatment was androgen plus low dose prednisolone 8/15 (53.3%) and 2nd ATG plus cyclosporine 7/15 (46.7%) with a median (range) subsequent response time of 6.9 (1 to 21) months.

Severe disease-related complications were reported among 12 patients. The most common was invasive fungal infection (8 of 12 patients) following by internal organ bleeding (3 of 12 patients) and bacterial septicemia (1 of 12 patients). Twenty patients (66.7%) developed treatment-related complications namely, ATG induced serum sickness among five patients (25%) and severe hirsutism and gum hypertrophy from cyclosporine among eight patients (40%).

With the median time follow-up of 4.3 years, 21 patients survived. Nine patients, eight patients with immunosuppressive therapy and one patient after BMT, died at the median time of 18 months after diagnosis. The major cause of death was severe infection (fungus and bacterial). No correlation was found between low ANC at diagnosis with treatment response (p-value = 0.803), disease and treatment-related complications (p-value = 0.172) and patient mortality (p-value = 0.923).

The five-year overall survival (OS) was 69.4% (95%CI: 0.49-0.82) among all patients and 72.9% (95%CI: 0.49-0.86) among patients receiving ATG with cyclosporine (Figure 1). Three of four patients underwent matched sibling allogeneic stem cell transplantation and survived without disease with a median follow-up time of 7.3 years (Range 3 to 10 years).

Discussion

As many related published studies showed the treatment of severe aplastic anemia, whether by matched sibling allogeneic stem cells transplantation or immunosuppression experienced improved clinical and long term survival for more than 25 years.[6-9] Our study is the first study to review the outcome of children with severe idiopathic aplastic anemia in the past 20 years treated in our institution with ATG plus cyclosporin, androgen plus low dose prednisolone and allogeneic stem cells transplantation. The response of treatment in the rabbit ATG plus cyclosporine group in our institute was similar to related international studies (the data showed same age group of population and severity of disease)[5]. The incidence of complications following initiation of immunosuppressive therapy such as serum sickness (25%) were similar to a related study

but the incidence of bacterial and fungal infection(75%) in our institute showed a higher rate more than another international study (approximately 56.4%).[4,10] Although matched sibling allogeneic stem cell transplantation is the recommended first-line treatment, only 4 of 30 patients (13%) had matched related donors and all proceeded to transplantation. For these reasons, immunosuppressive therapy consisting of ATG plus cyclosporine remains the most effective first-line treatment of patients with severe idiopathic aplastic anemia without matched siblings.

Conflict of interest

The authors declare they have no conflicts of interest to disclose.

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