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Natural History of Moderate Aplastic Anemia in Children

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Background. Moderate aplastic anemia (MAA) in children is a rare, idiopathic condition of bone marrow insufficiency that can resolve spontaneously, persist for months or years, or progress to severe aplastic anemia (SAA). We evaluated the rate of progression to SAA. ***Methods.*** We reviewed the records of 136 children referred for evaluation of bone marrow failure from 1978 to 2002 at St. Jude Children's Research Hospital. MAA was defined by a hypocellular bone marrow (<50%) and 2 or 3 cytopenias (absolute neutrophil count <1,500/mm^3, absolute reticulocyte count <40,000/mm^3, platelet count <100,000/mm^3) lasting at least 6 weeks. ***Results.*** Twenty-four patients met the criteria for MAA. At a median follow-up of 66 months (range, 10–293), 16 patients (67%) progressed to SAA, 5 (21%) had persistent MAA, and 3 (12%) had complete resolution of MAA. No risk factors for progression could be identified. ***Conclusions.*** When childhood MAA is treated with supportive care alone, 2/3 of patients progress to SAA. Pediatr Blood Cancer 2004;43:545–551. © 2004 Wiley-Liss, Inc.

Key words: bone marrow failure; moderate aplastic anemia; natural history; pediatric

INTRODUCTION

Moderate aplastic anemia (MAA) is an acquired condition of diminished bone marrow activity that leads to anemia, thrombocytopenia, and leukopenia. It can be precipitated by viral infections or medications, but in most cases the cause is unknown [1–9]. The disease can resolve spontaneously, persist as moderate bone marrow suppression, or progress to severe aplastic anemia (SAA). Standard treatment for MAA has been observation alone, and most hematologists offer immunosuppressive therapy or bone marrow transplantation only to patients who progress to SAA. The validity of this approach compared with early intervention remains unproven, since no randomized trials have been performed. If the rate of progression to SAA is high, it may be appropriate to use early immunosuppression to prevent progression to a more severe condition and the possible subsequent need for hematopoietic stem cell transplantation (HSCT). We performed this study to document the rate of progression of MAA to SAA and to identify risk factors for progression that would justify early therapy.

PATIENTS AND METHODS

After the study was approved by the Institutional Review Board, we reviewed the records of pediatric patients referred to St. Jude Children's Research Hospital from 1978 to 2002 for evaluation of suspected bone marrow failure to identify those with MAA. MAA was defined as bone marrow cellularity <50% and 2 or 3 cytopenias that persisted for 6 weeks or more: absolute neutrophil count (ANC) <1,500/mm^3, absolute reticulocyte count (ARC) <40,000/mm^3, platelet count <100,000/mm^3, without meeting criteria for SAA (bone marrow cellularity <30% and 2 or 3 cytopenias: ANC <500/mm^3, ARC <40,000/mm^3, platelet count <20,000/mm^3) [10]. The condition was defined as ''transient'' if it resolved completely in less than 6 weeks, regardless of the severity of cytopenias or bone marrow hypocellularity. The standard evaluation for bone marrow failure included a detailed medical history, physical examination, complete blood count, bone marrow aspirate and biopsy, cytogenetics, testing for paroxysmal nocturnal hemoglobinuria and Fanconi anemia, and hepatitis viral serology. Patient follow-up data was last updated March 31, 2003.

Potential risk factors for progression to SAA included race, sex, age, severity of cytopenias (WBC, ANC, ARC,

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platelet count), elevation of the red blood cell mean corpuscular volume (MCV), and the percentage of fetal hemoglobin. A Cox proportional hazards model was used to study the relationship of time to progression and the potential risk factors. Statistical analysis was conducted using S-Plus (MathSoft, Inc.) and the significance level was set at $P = 0.05$. Missing data were assumed to be random. Statistical analysis of the prognostic importance of the rate of decline of blood cell counts or time to the nadir of counts could not be performed because of the small number of patients and variable schedule of blood sampling.

RESULTS

A total of 136 cases of aplastic anemia were reviewed (Table I). Idiopathic acquired aplastic anemia was diagnosed in 112 patients (82%) and 24 (18%) met the criteria for moderate severity. The ages of the 24 patients ranged from 2 to 18 years (median, 8 years) (Table II). Ten (42%) were female; 19 were Caucasian, 3 African-American, 1 Asian, and 1 Hispanic. Of the 24 patients with MAA, 11 presented with symptomatic thrombocytopenia, 4 with symptomatic anemia, 6 with both of these cytopenias, 1 with dystrophic nails (but no other evidence of dyskeratosis congenita), and 2 with abnormalities found on a screening complete blood count. Of the 24, 2 lacked cytogenetic evaluation, 6 lacked paroxysmal nocturnal hemoglobinuria testing, and 3 lacked Fanconi anemia testing. In only one case (patient 5), did infectious hepatitis precede MAA. None of the patients were diagnosed with Fanconi anemia or PNH at the time they presented with MAA. Eleven of these have been reported previously [11]. An additional patient that had been included in the previous report is not included in the current study, since his bone marrow cellularity was found to be >50% when reviewed.

TABLE I. Patients Referred to St. Jude Children's Research Hospital for Evaluation of Suspected Bone Marrow Failure (1978–2002)

Diagnosis	Number
Idiopathic acquired aplastic anemia	112
Transient aplastic anemia	(1)
Mild aplastic anemia	(4)
Moderate aplastic anemia	(24)
Severe aplastic anemia	(80)
Unclassifiable aplastic anemia	(3)
Paroxysmal nocturnal hemoglobinuria	2
Fanconi anemia	19
Dyskeratosis congenita	3
Total	136

Transient aplastic anemia, idiopathic acquired aplastic anemia that resolves completely in less than 6 weeks. Mild aplastic anemia, bone marrow hypocellularity and two or three cytopenias that persist for 6 weeks or more, but not severe enough to meet criteria for moderate aplastic anemia (MAA). Moderate aplastic anemia, bone marrow cellularity <50% and two or three cytopenias that persist for 6 weeks or more: absolute neutrophil count <1,500/mm^3, absolute reticulocyte count <40,000/mm^3, platelet count <100,000/mm^3; but not severe enough to meet criteria for MAA. Severe aplastic anemia (SAA), bone marrow cellularity <30% and 2 or 3 cytopenias that persist for 6 weeks or more: absolute neutrophil count <500/mm^3, absolute reticulocyte count <40,000/mm^3, platelet count <20,000/mm^3. Unclassifiable aplastic anemia, data insufficient to make a diagnosis of transient, mild, moderate, or SAA (e.g., bone marrow cellularity not documented); or other causes of bone marrow aplasia not adequately excluded (e.g., lack of PNH or Fanconi anemia tests).

Patients were treated with supportive care alone, except for three patients: two received prednisone for treatment of presumed immune thrombocytopenic purpura (ITP) (patient 5 in Table II) or Evans syndrome (patient 13) and one (patient 11) was treated with prednisone for 4 months before progression of MAA to SAA. Patient 5 had a normocellular bone marrow at presentation and was diagnosed with Evans syndrome. He was treated with oral prednisone for 1 month which was associated with improvement in ARC but a decrease in platelet count. Prednisone was stopped when MAA was diagnosed on the basis of persistent trilineage cytopenia and hypocellular bone marrow. Patient 13 was initially diagnosed with ITP, and was referred when he did not respond to 10 weeks of oral prednisone therapy. Bone marrow was not examined at the time of presentation, but at the time of referral, a bone marrow examination revealed amegakaryocytic thrombocytopenia, a condition with a known risk for progression to aplastic anemia [12,13]. Ten weeks later MAA was diagnosed.

With a median follow-up of 66 months, 16 patients (67%) progressed to SAA at a median of 9.5 months (range, 2–290 months) after diagnosis. Five (21%) had persistent MAA at a median of 32 months (range, 25–118 months), and 3 (12%) had complete resolution of MAA at a median of 7 months (range, 2–11 months) after diagnosis (Table III). Figure 1 shows the Kaplan–Meier estimate and the 95% confidence interval for progression-free survival at 36 months. The proportion whose MAA resolved over time is also shown in Figure 1. The 3-year progression-free survival was 43.5% (standard error, 24.3%). None of the potential risk factors were significantly associated with disease progression (Table IV), except for a marginal association of a lower platelet count nadir during the initial six weeks ($P = 0.07$). The relative risk of progression was 1.8 (95% confidence interval, 1 to 3.4) for every 20,000/mm^3 decrement in the platelet count nadir; for example, a patient with a platelet count nadir of 30,000/mm^3 would have an estimated 80% higher risk of progression than one with a nadir of 50,000/mm^3. There was no significant correlation between bone marrow cellularity or the percentage of hemoglobin F at diagnosis, nor in the nadir of the ANC and the subsequent clinical course (data not shown).

TABLE II. Clinical Features at Diagnosis of 24 Children With MAA

Pt no	Sex	Race	Age at diagnosis (years)	Lowest WBC ($\times$1,000/mm^3)	Lowest ANC (per mm^3)	Lowest platelet count ($\times$1,000/mm^3)	Lowest ARC ($\times$1,000/mm^3)	Highest MCV (fL)	Comments[a]
1	M	White	1.7	2.1	252	5	11.6	95	
2	F	White	6.3	2.8	56	1	34.9	106	Not tested for PNH at initial work-up
3	F	Asian	6.6	2.7	532	28	37.6	96	Not tested for PNH, Fanconi, or peripheral blood cytogenetic abnormalities at initial work-up; parents work with radioactive materials
4	M	White	14.6	2.2	748	11	5.1	94	
5	M	White	6.2	1.4	840	0	28.6	112	Infectious hepatitis 3 months prior to MAA, treated for Evans syndrome with prednisone for 1 month prior to diagnosis of MAA
6	F	White	8.2	2.9	1218	42	ND	101	
7	M	White	5.0	1.3	130	246	14.2	108	
8	F	Black	10.1	2.5	850	86	72.2	92	Not tested for Fanconi or peripheral blood cytogenetic abnormalities at initial work-up; mononucleosis 3 months prior to MAA
9	M	White	4.8	3.5	703	9	42.5	100	Not tested for PNH at initial work-up
10	F	White	8.0	2.8	578	5	25.9	109	
11	F	White	11.2	1.3	714	15	49.4	99	Not tested for PNH or Fanconi at initial work-up; treated with prednisone at diagnosis of MAA
12	F	Black	14.0	1.3	52	23	22.2	97	Treated with phenobarbital and macrodantin
13	M	White	3.5	2.8	784	8	24.8	91	Treated for ITP with prednisone for 10 weeks before MAA diagnosis
14	M	White	12.9	1.3	549	20	42.0	102	
15	M	Hispanic	9.7	2.7	567	60	17.7	91	
16	F	White	16.4	2.3	868	35	28.9	110	Treated with a ‘‘weight loss medication’’ prior to MAA
17	F	White	12.9	3.6	1044	6	20.5	102	
18	M	White	18.4	2.1	476	1	15.1	100	
19	M	White	12.1	2.3	920	35	33.3	111	Not tested for PNH at initial work-up; dyskeratotic fingernails and toenails, but no other evidence for Dyskeratosis congenita
20	M	White	8.2	17	357	28	9.6	—	Café au lait spots and short stature
21	F	White	5.1	17	440	36	25.0	102	Imperforate anus, single kidney with ureteral blockage; parvovirus B-19 IgM positive; father polycythemic
22	M	White	3.4	43	817	43	55.7	99	Not tested for PNH at initial work-up
23	M	Black	7.6	31	1333	47	56.2	101	
24	M	White	8.2	29	672	80	2.1	101	

M, male; F, female; MAA, moderate aplastic anemia; ITP, immune thrombocytopenic purpura; ANC, absolute neutrophil count; ARC, absolute reticulocyte count; PNH, paroxysmal nocturnal hemoglobinuria.

[a]The standard evaluation for bone marrow failure included cytogenetics and testing for paroxysmal nocturnal hemoglobinuria and Fanconi anemia, unless otherwise indicated.

TABLE III. Course of the Disease and Outcomes for Children With MAA

Pt no	Outcome	Months from diagnosis to outcome	Treatment for MAA	Treatment after progression to SAA	Survival status	Follow-up time from diagnosis (months)	Comments (unusual features)
1	Resolved	2.0	None	—	Alive	66	
2	Resolved	6.6	None	—	Alive	10	
3	Resolved	11	None	—	Alive	33	
4	MAA	23	None	—	Alive	23	
5	MAA	27	Prednisone	—	Alive	27	
6	MAA	31	None	—	Alive	31	
7	MAA	45	None	—	Alive	45	
8	MAA	120	Prednisone	—	Alive	120	
9	SAA	1.9	None	ATG/Prednisone then CsA/Oxymetholone	Expired	24	Respiratory failure secondary to *Aspergillus fumigatus* pneumonia
10	SAA	2.1	None	HSCT (matched sibling donor)	Alive	62	
11	SAA	2.3	Prednisone	ATG, then Danazol + CsA	Alive	216	
12	SAA	2.6	None	GMCSF, then ATG	Alive	120	
13	SAA	2.7	None	ATG/Prednisone	Alive	117	
14	SAA	3.6	None	HSCT (matched sibling donor)	Alive	89	
15	SAA	4.3	None	HSCT (matched sibling donor)	Alive	32	After progression to SAA, developed MDS, then underwent HSCT
16	SAA	7.5	None	CsA/ATG/GCSF/Prednisone	Alive	23	
17	SAA	12	None	HSCT (matched sibling donor)	Alive	66	Developed paroxysmal nocturnal hemoglobinuria
18	SAA	18	None	ATG/nodal irradiation	Alive	152	
19	SAA	20	None	CsA/ATG/GMCSF, then HSCT (matched unrelated donor)	Expired	47	Died of adult respiratory distress syndrome and multi-organ failure 4 months after transplant. Autopsy did not identify a specific causal agent.
20	SAA	23	None	ATG, then ATG + methylprednisolone	Alive	166	Initially negative for Fanconi anemia, but found to be mosaic when retested years later
21	SAA	30	None	ATG, then HSCT (matched sibling donor)	Alive	181	
22	SAA	101	None	ATG, then HSCT (matched unrelated donor)	Alive	194	Developed paroxysmal nocturnal hemoglobinuria
23	SAA	128	None	CsA/ATG/GMCSF/Prednisone	Alive	147	
24	SAA	290	None	HSCT (matched sibling donor)	Alive	293	Developed MDS, then underwent BMT

MAA, moderate aplastic anemia; SAA, severe aplastic anemia; MDS, myelodysplastic syndrome; HSCT, hematopoietic stem cell transplantation; Outcomes: Resolved, resolution of MAA; MAA, persistent MAA; SAA, progression to SAA; ATG, anti-thymocyte globulin; CsA, cyclosporine A; GCSF, granulocyte colony-stimulating factor; GMCSF, granulocyte–monocyte colony-stimulating factor.

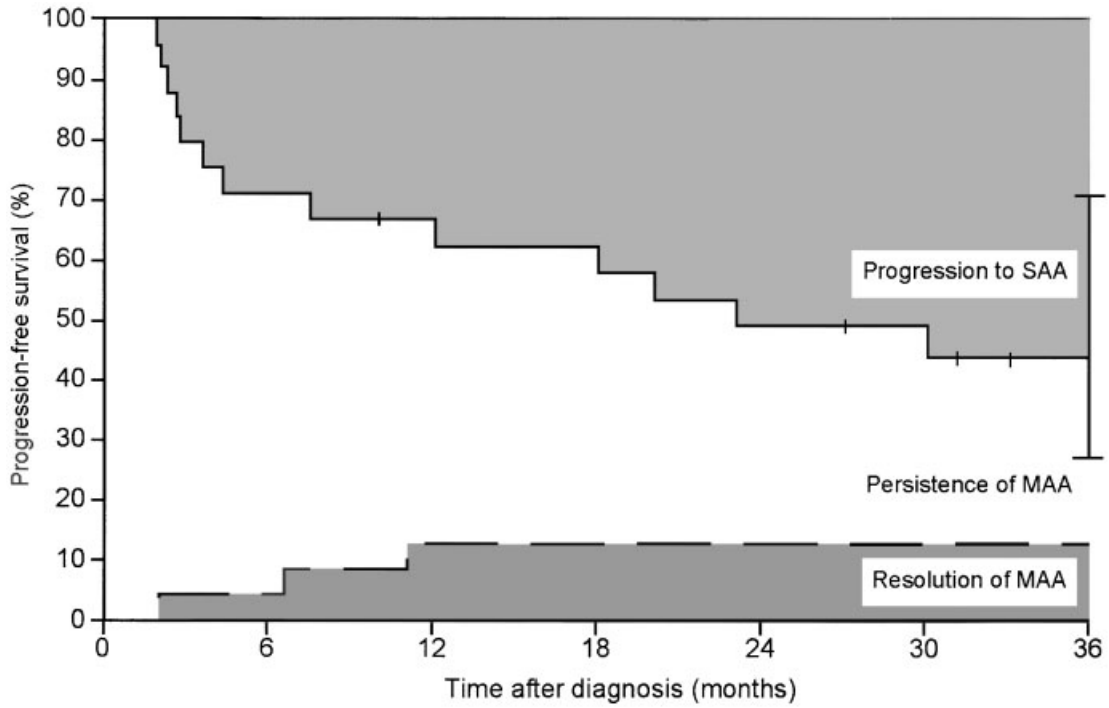

Fig. 1. Progression-free survival of children with moderate aplastic anemia. Kaplan–Meyer curve of progression to severe aplastic anemia is shown by the solid line (n = 16). Resolution of aplastic anemia is shown by the dashed line (n = 3). Thirty-six months after the diagnosis of moderate aplastic anemia, the progression-free survival was 43 ± 24%.

Patients were followed for a median of 66 months (range, 10–293 months). Eight patients with resolution or persistence of MAA are currently alive. Of 16 patients who progressed to SAA, 8 underwent HSCT and 2 of these died 22 and 26 months after progression to SAA. One patient developed myelodysplastic syndrome after persistent MAA for 23 years. Patients 17 and 22 were diagnosed with PNH 1 and 8 years after the diagnosis of MAA.

DISCUSSION

Presenting Features and Diagnosis of MAA

Although Evans syndrome has been reported after bone marrow transplantation for SAA [14], it has not been reported to precede MAA. Patients 5 and 13 suggest that immune thrombocytopenic purpura, Evans syndrome, and MAA may represent various syndromes within a

TABLE IV. Potential Risk Factors for Progression to SAA for Pediatric Patients With MAA

Putative risk factor	Patients who progressed to SAA	Patients who did not progress to SAA	*P*-value
Race (White:Black:Other)	13:2:1	6:1:1	0.56
Sex (male:female)	10:6	4:4	0.49
Mean age at diagnosis (years)	9.8	7.3	0.14
Complete blood count values during the initial 6 weeks of observation			
Mean of the lowest WBC for each patient (/mm^3)	2,481	2,238	0.79
Mean of the lowest ANC for each patient (/mm^3)	680	578	0.73
Mean of the lowest platelet count for each patient (/mm^3)	28,188	52,375	0.07
Mean of the lowest ARC for each patient (/mm^3)	29,440	29,192	0.28
Mean of the highest MCV for each patient (fL)	101	100.5	0.60

WBC, white blood cell count; ANC, absolute neutrophil count; ARC, absolute reticulocyte count; MCV, erythrocyte mean cell volume.

spectrum of autoimmune conditions that target antigens on hematopoietic cells and their precursors, a supposition consistent with reports of concurrent immune thrombocytopenia and aplastic anemia during pregnancy or with interferon therapy for hepatitis C [15,16]. Two patients (17 and 22) were later diagnosed with PNH. Patient 17 did not have laboratory evidence of PNH at the time of diagnosis and patient 22 was not tested, so whether PNH was the cause or the result of bone marrow insufficiency was not clear.

Reported Outcome of Moderate Aplastic Anemia

Only two studies of MAA in children have been published [11,17] and little is known about its natural history. In the current review of our 24-year experience with pediatric patients with MAA, we found an alarmingly high (67%) rate of progression to SAA. Although only two patients died, eight were treated with immunosuppression and eight with HSCT, with their attendant morbidity and risk for late toxicity or relapse. In a study of 111 Japanese children with MAA diagnosed from 1966 to 1985, follow-up information was available on 99 patients [17]. Of these, 25 recovered completely, 35 died, and 39 had intermediate outcomes (partial recovery, maintenance on medication, and/or transfusion dependence). Overall survival was 65%, but patients from the later treatment era (diagnosed from 1976 to 1985) had a 74% survival, compared to 54% in the previous era. Of 12 pediatric patients with MAA seen at St. Jude Children's Research Hospital between 1978 and 1991, three required no treatment, four required supportive care including transfusion for less than 6 months, and five progressed to SAA [11]. Although all patients in that report were long-term survivors, two of the seven patients who did not progress to SAA had persistent cytopenias and one developed myelodysplastic syndrome (patient 24 in the current report).

Summary of Findings of This Study

We did not identify any prognostic factors associated with a higher (or lower) risk of progression. Therefore, if early intervention is considered, it must be directed toward all children with MAA. The timing of progression was unpredictable; some patients progressed to SAA within a few months of diagnosis, while others progressed after years of persistent MAA, suggesting that intervention should be considered even in patients with MAA that has persisted for years. None of the three patients whose MAA resolved completely had recurrence of MAA.

Treatment of Childhood MAA

There have been no clinical trials of therapy for pediatric MAA, thus the indications for treatment and the optimal immunosuppressive regimen are not well defined. In patients with SAA and no suitable bone marrow donor, immunosuppression is the most effective treatment. The best results have been achieved with combination therapy that included antilymphocyte or antithymocyte globulin (ALG or ATG) and cyclosporine [1,20–26]. In patients with SAA, this combination was superior to ALG alone in a randomized, multicenter trial that enrolled 84 patients with SAA and non-severe aplastic anemia (nSAA) [22,27]. In this study, 41 patients received ALG and methylprednisolone and 43 received ALG, methylprednisolone, and cyclosporine. At 4 months, 70% of patients responded to three-drug treatment compared to 41% of patients in the two-drug control group ($P = 0.015$). In subgroup analysis, the improved response in patients treated with cyclosporine applied to patients with SAA ($P = 0.011$), but not to those with nSAA ($P = 0.6$). Furthermore, the difference in response rate did not translate into a survival advantage for patients with either SAA or nSAA, and the actuarial survival at 11.3 years was 58% in the cyclosporine group and 54% in the control group ($P = 0.6$). Cyclosporine had substantial but reversible side effects. The authors concluded that for patients with SAA, treatment with ALG, methylprednisolone, and cyclosporine produced a higher rate of response than ALG plus methylprednisolone without cyclosporine, but nSAA patients did not benefit from the addition of cyclosporine.

Marsh et al. [28] studied adults and children with nSAA and demonstrated better response rates to antithymocyte globulin (ATG) plus cyclosporine than to cyclosporine alone. They enrolled 115 patients (97 adults, 18 children) with nSAA, defined as hypocellular bone marrow, a neutrophil count $\geq 0.5 \times 10^9$/L, and red cell or platelet transfusion dependence, in a randomized trial of cyclosporine versus cyclosporine plus ATG. These patients generally had more severe aplasia than the patients with MAA in our study. Forty-six percent of patients treated with cyclosporine alone had a complete or partial response, compared to 74% of patients treated with cyclosporine plus ATG ($P = 0.02$). They concluded that the course of nSAA was favorably modified by more aggressive immunosuppression using ATG plus cyclosporine compared to cyclosporine alone. Eighteen children participated in the study, and they too had a better response to ATG plus cyclosporine (87%) than to cyclosporine alone (30%, $P = 0.04$) [29].

In summary, in both adults and children with ''non-severe'' aplastic anemia, the response to ATG plus cyclosporine was better than the response to cyclosporine alone, but the response to ALG plus cyclosporine was no better than the response to ALG alone. Therefore, if children with MAA are treated with immunosuppression, ATG (or ALG) should be included in the treatment regimen. Whether cyclosporine confers additional benefit in these patients is unknown.

When childhood MAA is treated with supportive care, 67% of patients progress to SAA, suggesting the need to consider early therapy with immunosuppression. However, because the benefits of early intervention with immunosuppression or hematopoietic stem cell transplantation for pediatric patients with MAA are not known and the risks of these treatments are considerable, a randomized clinical trial is needed.

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