Treatment and response of autoimmune cytopenia occurring after allogeneic hematopoietic cell transplantation in children

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Background
Autoimmune cytopenia (AIC) is a rare complication of allogeneic hematopoietic cell transplantation (HCT). In this study, we reviewed the diagnosis, treatment and response to therapy for pediatric patients with post-HCT AIC at our institution.

Methods
Of the 292 allogeneic HCTs performed from January, 2011 to December, 2015 at the Department of Pediatrics, The Catholic University of Korea, seven were complicated by post-HCT AIC, resulting in an incidence of 2.4%.

Results
All seven patients with post-HCT AIC had received unrelated donor transplant. Six of seven patients had a major donor-recipient blood type mismatch. The subtypes of AIC were as follows: immune thrombocytopenia (ITP) 2, autoimmune hemolytic anemia (AIHA) 2, Evans syndrome 3. Median time from HCT to AIC diagnosis was 3.6 months. All but one patient responded to first line therapy of steroid±intravenous immunoglobulin (IVIG), but none achieved complete response (CR) with this treatment. After a median duration of treatment of 15.3 months, two patients with ITP achieved CR and five had partial response (PR) of AIC. Five patients were treated with rituximab, resulting in the following response: 2 CR, 2 PR, 1 no response (NR). Median time to response to rituximab was 26 days from first infusion. All patients are alive without event.

Conclusion
Post-HCT AIC is a rare complication that may not resolve despite prolonged therapy. Rapid initiation of second line agents including but not limited to B cell depleting treatment should be considered for those that fail to achieve CR with first line therapy.

Key Words
Autoimmune cytopenia, Autoimmune hemolytic anemia, Immune thrombocytopenia, Hematopoietic cell transplantation, Rituximab

INTRODUCTION

A rare but important complication of allogeneic hematopoietic cell transplantation (HCT) is autoimmune disease, the etiology of which remains unclear [1]. Autoimmune cytopenia (AIC), including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), is a manifestation of such autoimmune disease. Due to the rarity of post-HCT AIC, the literature on this disease is limited, especially as pertains to the pediatric population. Reported incidence of post-HCT AIC in children varies from 2.1 to 6%, either studied for AIC as a whole or for subsets such as AIHA [2-4]. Data on the outcome for post-HCT AIC is conflicting, with some studies indicating an overall good response to therapy [4, 5], while others show that a complete response (CR) to therapy is obtained only in a minority of patients, with increased mortality as a result of this complication [2, 6]. Significant risk factors for post-HCT AIC made apparent from these studies include HCT for a non-malignant disease, transplant from an unrelated donor, and chronic graft-versus-host disease (GVHD) after transplant [3, 7, 8].

For patients who do not achieve a CR of AIC with first-line therapy of steroid and intravenous immunoglobulin (IVIG),
the options for treatment are limited. Numerous studies, however, have shown that rituximab, the anti-CD20 monoclonal antibody, is effective in the treatment of post-HCT AIC that fails to resolve with first-line therapy [9-13].

In this study, we analyzed patients diagnosed with post-HCT AIC at our institution to determine the features of this disease in our patients, and evaluate the treatment course and overall response to therapy. We also analyzed the response to rituximab for those who received this antibody therapy.

MATERIALS AND METHODS

Patient group

We retrospectively reviewed the medical records of patients who received allogeneic HCT at the Department of Pediatrics, The Catholic University of Korea from January, 2011 to December, 2015 to evaluate for possible post-HCT AIC.

Transplant regimen

The details of our transplant protocol have previously been shown elsewhere [14, 15]. In brief, all unrelated donors were matched at high resolution typing for HLA-A, B, C and DRB1 alleles, except for cord blood (CB) units which were matched at antigen level for HLA-A, B and DRB1. The conditioning regimen for patients with acute myeloid leukemia (AML) consisted of busulfan (Bu) and fludarabine (Flu), with rabbit anti-thymocyte globulin (ATG) given for unrelated donor transplants. Flu, cyclophosphamide (Cy) and ATG were given to severe aplastic anemia (SAA) patients receiving either matched sibling or unrelated donor transplants. Flu, cyclophosphamide (Cy) and ATG were given to severe aplastic anemia (SAA) patients receiving either matched sibling or unrelated donor transplants.

Diagnosis of AIC

Post-HCT AIHA was considered if the patient showed an unexplained fall in hemoglobin combined with reticulocytosis. Diagnosis was confirmed by positive direct antiglobulin test. ITP was diagnosed if the patient showed a rapid decrease in the platelet count, the etiology of which remained unclear, normal peripheral blood morphology except for thrombocytopenia, and unremarkable bone marrow findings, including normal megakaryopoiesis.

Table 1. Transplant characteristics of patients diagnosed with post-transplant autoimmune cytopenia.

| Patient | Gender | Age at transplant (yrs) | Diagnosis | Donor type | Donor gender | Cell source | Conditioning | HLA compatibility | ABO compatibility | N of previous transfusions |
|---------|--------|-------------------------|-----------|------------|--------------|-------------|--------------|------------------|---------------------|-------------------------|
| Patient 1 | Female | 3.2 | SAA | Unrelated | Female | PBSC | Flu-Cy-ATG | 7/8 | Major and minor | 8 |
| Patient 2 | Male | 12.6 | AML | Unrelated | Male | CB | Bu-Flu-ATG | 6/6, 5/6 | Major | 149 |
| Patient 3 | Female | 9.5 | SAA | Unrelated | Male | PBSC | Flu-Cy-ATG | 8/8 | Match | 14 |
| Patient 4 | Male | 11.7 | SAA | Unrelated | Male | PBSC | Flu-Cy-ATG | 7/8 | Major | 16 |
| Patient 5 | Male | 1.3 | WAS | Unrelated | Female | PBSC | Bu-Cy-ATG | 8/8 | Major and minor | 1 |
| Patient 6 | Male | 16.2 | AML | Unrelated | Female | PBSC | Bu-Flu-ATG | 8/8 | Major | 36 |
| Patient 7 | Female | 9.5 | MDS | Unrelated | Male | PBSC | Flu-Cy-ATG | 8/8 | Major | 12 |

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*High-resolution typing of HLA-A, HLA-B, HLA-C, and HLA-DR. For cord blood transplants, matching was done at the antigen level for HLA-A, HLA-B, and HLA-DR. *Categorized as match/major mismatch/minor mismatch/major and minor mismatch. *Number of transfusions prior to transplantation. Abbreviations: AML, acute myeloid leukemia; ATG, rabbit anti-thymocyte globulin; Bu, busulfan; CB, cord blood; Cy, cyclophosphamide; Flu, fludarabine; MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cells; SAA, severe aplastic anemia; WAS, Wiskott-Aldrich syndrome.
patients requiring HCT were as follows: SAA 3, AML 2, MDS 1, and WAS 1 (Table 1). Four of the patients received nonmyeloablative conditioning prior to transplant. Of note, all seven patients received HCT from an unrelated donor (peripheral blood stem cell transplant (PBSC) 6, cord blood transplant (CBT) 1). Excepting one patient, all patients showed either a major donor-recipient blood type mismatch (N=4) or both major and minor mismatch (N=2). The median number of transfusions prior to transplant was 14 (range, 1–149). The median cell doses for the six patients who received PBSC were as follows: total nucleated cells (TNC) $14.6 \times 10^7$/kg (range, 11.2–24.1×10^7/kg), mononuclear cells (MNC) $11.6 \times 10^7$/kg (range, 7.4–15.4×10^7/kg), CD34+ $8.4 \times 10^7$/kg (range, 4.9–13.2×10^7/kg), CD3+ $56.4 \times 10^7$/kg (range, 26.2–75.8×10^7/kg).

**Diagnosis of post-HCT AIC**

The types of AIC diagnosed in the seven patients were as follows: ITP 2, AIHA 2, Evans syndrome 3 (Table 2). All patients were diagnosed with AIC within one year of transplant, with a median time from HCT to diagnosis of AIC of 3.6 months (range, 3.1–10.7 mo). Five patients were diagnosed within six months of HCT. All five patients with an AIHA component in their AIC showed positive direct and indirect Coombs test results. Donor chimerism, as determined by studies of PB short tandem repeat polymerase chain reaction (STR-PCR), indicated complete donor chimerism at the time of AIC diagnosis (median donor chimerism 100%, range, 95.8%–100%). Patient 6 had been diagnosed with grade II acute skin and gastrointestinal GVHD five months prior to the diagnosis of AIC. However, none of the other patients had a history of either acute or chronic GVHD prior to or at the time of AIC diagnosis.

**Table 2. Diagnosis of post-transplant AIC.**

| Type of AIC | Time to AIC (mo) | Donor chimerism at AIC diagnosis (%) | Coombs test (direct/indirect) |
|------------|------------------|--------------------------------------|------------------------------|
| Patient 1  | Evans syndrome   | 3.2                                  | 95.8                         | 4+/4+                        |
| Patient 2  | AIHA             | 10.7                                 | 100.0                        | 4+/3+                        |
| Patient 3  | ITP              | 3.6                                  | 100.0                        |                              |
| Patient 4  | Evans syndrome   | 3.1                                  | 98.0                         | 4+/2+                        |
| Patient 5  | AIHA             | 9.7                                  | 99.0                         | 4+/3+                        |
| Patient 6  | Evans syndrome   | 5.3                                  | 100.0                        | 4+/2+                        |
| Patient 7  | ITP              | 3.6                                  | 100.0                        |                              |

*aFrom the date of hematopoietic cell transplantation.
Abbreviations: AIC, autoimmune cytopenia; AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenia.

**Table 3. Treatment and response of post-transplant AIC.**

| N of drugs given | Order of treatment | Time to first response (days) | Medication used for first response | Overall AIC response | Time to resolution (mo) | Medication used for resolution |
|------------------|--------------------|-------------------------------|-----------------------------------|----------------------|-------------------------|-------------------------------|
| Patient 1        | 6 Steroid, IVIG → rituximab → azathioprine → 6-MP → splenectomy → MMF | 13                             | Steroid, IVIG                   | PR (ITP: CR, AIHA: PR) |                         |                               |
| Patient 2        | 2 Steroid → rituximab | 46                             | Steroid                          | PR                   |                         |                               |
| Patient 3        | 4 Steroid, IVIG → azathioprine → rituximab | 19                             | Steroid, IVIG                   | CR                   | 2.3                     | Rituximab                    |
| Patient 4        | 3 Steroid → rituximab → MMF | 54                             | Rituximab                        | PR (ITP: PR, AIHA: CR) |                         |                               |
| Patient 5        | 2 Steroid → MMF     | 22                             | Steroid                          | PR                   |                         |                               |
| Patient 6        | 1 Steroid           | 24                             | Steroid                          | PR (ITP: CR, AIHA: PR) |                         |                               |
| Patient 7        | 3 Steroid, IVIG → rituximab | 14                             | Steroid, IVIG                   | CR                   | 6.1                     | Rituximab                    |

*aThe doses of medication administered were as follows: steroid, 1–2 mg/kg/day; IVIG, 1 g/kg/day for 2 days; rituximab, 375 mg/m²/dose weekly for 4 consecutive weeks; azathioprine, 1–4 mg/kg/day daily; 6-MP, 60 mg/m²/day daily; and MMF, 250–600 mg/m²/dose twice daily orally. b,c From the date of AIC diagnosis.

Abbreviations: 6-MP, mercaptopurine; AIC, autoimmune cytopenia; AIHA, autoimmune hemolytic anemia; CR, complete response; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; PR, partial response.
to response was 22 days (range, 13–54 days). During the entire follow-up period, each patient was treated with a median of three different medications (range, 1–6). The doses of the other medications administered were as follows: rituximab, 375 mg/m²/dose weekly for four consecutive weeks; azathioprine, 1–4 mg/kg/day daily; 6-mercaptopurine, 60 mg/m²/day daily; mycophenolate mofetil (MMF), 250–600 mg/m²/dose twice daily orally. Splenectomy was performed in Patient 1 with Evans syndrome whose ITP component had previously resolved, but whose AIHA remained in steroid-dependent PR. The AIHA in this patient failed to resolve despite splenectomy. At a median of 17.3 months follow-up since diagnosis of AIC (range, 9.6–50.3 mo), two patients had CR and five patients had PR of AIC. The two patients with CR both had ITP which resolved with rituximab at 2.3 and 6.1 months after initial diagnosis of ITP respectively. The median duration of treatment for all patients was 15.3 months (range, 2.3–50.3 mo).

Treatment of post-HCT AIC using rituximab
Five of the seven patients were treated with rituximab at a median of 2.3 months from diagnosis of AIC (range, 0.7–16.8 mo) (Table 4). All five patients received the four scheduled doses of rituximab without major toxicity. The response to rituximab was as follows: 2 CR (2 patients with ITP), 2 PR, 1 NR. Of note, the median time from start of rituximab therapy to response for the four patients who showed PR or above was 26 days (range, 15–34 days).

Survival
At a median duration of follow-up of 27 months since HCT (range, 13.1–53.5 mo) all patients are alive without event. Of the five patients with PR, four remain on therapy for AIC at last follow-up, two patients on steroid and two on MMF. Patient 4 with Evans syndrome who showed CR of AIHA and NR of ITP had MMF stopped 12.8 months after diagnosis of post-HCT AIC despite thrombocytopenia. At last follow-up, this patient’s ITP had improved to PR status.

**DISCUSSION**

In this study, we reviewed the diagnosis and response to therapy for patients with post-HCT AIC in a cohort of allogeneic HCT recipients who received transplant during a five year period at our institution. Due to the rarity of the disease, the number of AIC patients included in our study is small. However, some important points can still be drawn from our data.

Our post-HCT AIC incidence of 2.4% was similar to the 2.1% reported from a recent pediatric study of 1,574 patients [3], and underscores that AIC after transplant is rare. In terms of the transplant-related characteristics of our patients with AIC, we emphasize that all seven patients received an unrelated donor transplant. As a result, all patients had received ATG as part of the conditioning regimen. Previous studies showed that an unrelated donor transplant is a risk factor for post-HCT AIC, and our study also supports this observation [3, 6, 7]. Within the framework of unrelated HCT, the immunomodulation caused by ATG therapy may be a causative factor in the subsequent development of AIC [19]. We also note that six of the seven patients showed at least a major blood type mismatch including all patients with an AIHA component, indicating that donor-recipient blood type disparity may also be a risk factor for AIC. In contrast to other studies that found chronic GVHD to be a significant factor for AIC [7, 8], none of the patients had symptomatic GVHD at the time of AIC diagnosis, and only one patient had previously been diagnosed with acute GVHD.

In terms of the onset of AIC, the median time to diagnosis was 3.6 months after HCT, with the majority diagnosed within six months of transplant, indicating that this complication occurred relatively early in the transplant course. All patients received first line therapy consisting of steroid±IVIG, resulting in six patients achieving overall PR and one patient with no response. Hence, first line treatment succeeded in stabilizing the complete blood count (CBC), but did not result in full resolution of AIC. Median time to response after treatment initiation was 22 days, consistent with therapy with the initial dose of medication for several weeks prior to attempting medication taper.

The overall response to treatment was less than optimal. At a median follow-up of 17.3 months since diagnosis of AIC only two patients had achieved resolution of AIC without further therapy. Treatment was significant both in terms of the mean number of agents used (N=3), and the median duration of treatment, that is 15.3 months. CR was achieved

| Table 4. Rituximab treatment of patients with post-transplant AIC. |
|-------------------------------------------------|
| Time to first response (days) |
| Concurrent medication |
|---|---|
| Patient 1 | 16.8 | 4 | NR | Steroid |
| Patient 2 | 7.0 | 4 | PR | Steroid |
| Patient 3 | 1.7 | 4 | CR | Steroid |
| Patient 4 | 0.7 | 4 | PR | Steroid |
| Patient 7 | 2.3 | 4 | CR | Steroid |

*From the date of AIC diagnosis. †From the start of rituximab treatment. Abbreviations: AIC, autoimmune cytopenia; CR, complete response; NR, no response; PR, partial response.
in two ITP patients with the use of rituximab.

Although five patients underwent rituximab therapy without major complications, the response was suboptimal when compared to previous reports [9, 20], with none of the patients with an AIHA component achieving CR. Both of the ITP patients who received rituximab achieved CR with this therapy, suggesting that rituximab may be more effective in the treatment of the ITP subtype of post-HCT AIC rather than AIHA, although the small number of treated patients precludes firm conclusions. Importantly, the median time from start of rituximab therapy to response was 26 days, indicating that an average response allowing for taper of concurrent medication was observed after the planned four infusions. These data should allow some insight into whether a response to rituximab should be observed, and for how long a patient should be followed before implementing another therapy.

It is noteworthy that one patient with Evans syndrome achieved CR of AIHA with MMF, and two patients achieved an overall PR of AIHA with MMF treatment and remain on MMF at last follow-up. MMF has been reported to be an effective agent in AIC patients unresponsive to steroid treatment, and may be considered early during the course of AIC therapy, suggesting that rituximab may be more effective in the treatment of the ITP subtype of post-HCT AIC rather than AIHA, although the small number of treated patients precludes firm conclusions. Importantly, the median time from start of rituximab therapy to response was 26 days, indicating that an average response allowing for taper of concurrent medication was observed after the planned four infusions. These data should allow some insight into when a response to rituximab should be observed, and for how long a patient should be followed before implementing another therapy.

A recent pediatric study on post-HCT AIHA showed a favorable outcome with 80% of patients achieving CR [4]. In contrast, although none of our patients died after transplant, the overall clinical course of post-HCT AIC indicated a transplant-related complication that failed to resolve despite prolonged treatment, a characteristic supported by other studies [2, 22]. As well as MMF, second line therapies that have been reported to be effective in the post-HCT setting include romiplostim for ITP and sirolimus for AIHA [23, 24].

The main limitations of our study include its retrospective nature, and the small number of patients with AIC, limiting valid analysis of risk factors for AIC and allowing for mostly descriptive data. We also underscore that our response criteria, based on the ability to taper or stop therapy, may be stricter than criteria based on absolute values of hemoglobin or platelet used in other studies [18, 25], resulting in both a lengthier time to response in our analysis and a fewer number of patients with CR at last follow-up. We believe that such a criteria better reflects the primary goal of not only improving the CBC values, but also stopping AIC therapy in order to minimize treatment-related morbidity, than a criteria based solely on CBC values, improvement of which may or may not be transient.

In summary, we found a 2.4% incidence of AIC in our allogeneic HCT recipient cohort. Unrelated donor transplant, possibly in the context of ATG use during conditioning, and major blood type mismatch were found in the majority of AIC patients. Despite prolonged therapy with multiple agents including rituximab, only two patients achieved CR of disease. Post-HCT AIC should be recognized as a rare but serious complication of HCT that may not resolve with steroid therapy. In such cases, the rapid initiation of second line agents including but not limited to B cell depleting treatment should be considered.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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