Long-Term Remission and Bone Marrow Findings in Children with Severe Aplastic Anemia Immunosuppressed with High Doses of Cyclophosphamide

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Abstract

Background: Most cases of aplastic anemia are acquired and of autoimmune etiology. Treatment of patients lacking a stem cell donor habitually consists of two curses of immunosuppression with anti-thymocyte globuline plus cyclophosphine (ATG/CsA), whereas intensive immunosuppression consisting exclusively of high doses of cyclophosphamide (HDCY) has been successfully employed mostly in adults, detailed long-term information on children receiving HDCY is lacking.

Patients and methods: Five children suffering from severe acquired aplastic anemia and without an HLA-compatible stem cell donor were immunosuppressed with high-dose cyclophosphamide (HDCY) at a total dose of 200 mg/kg over four days. Granulocyte colony-stimulating factor (G-CSF) was administered at 5 µg/kg/day until sustained neutrophil and platelet count recovery. The surviving patients were followed-up for twelve years and their bone marrows examined at this time.

Results: Three of the five children obtained a complete sustained hematological remission. Current ages are 17, 19 and 27. After twelve years of follow-up two patients have normal hematological values, with no relapse nor clonal or displasic hematological disorders, their bone marrow aspirate was morphologically normal, whereas bone marrow trephine biopsy histopathology demonstrated a reduced cell content to about 60% of normal. One patient developed myelodisplasia 12 years after HDCY and currently he is being considered for a bone marrow transplant.

Conclusions: Sustained long-term trilineage hematopoiesis can be rescued in children suffering from SAA employing HDCY as the only immunosuppressor; the bone marrow did not fully recuperate its normal cellularity after twelve years post-treatment, meliodysplasia can develop more than ten years after HDCY.

Keywords: Aplastic anemia; Antithymocyte globuline; Bone marrow; Cyclophosphamide; G-CSF; Immunosuppression

Introduction

With the exception of the reduced group in which an initiating event is documented, the vast majority of severe acquired aplastic anemia (SAA) cases are autoimmune, secondary to exposure to a self, chemical or viral antigen [1,2]. The fact that the majority of SAA patients respond to immunosuppressive therapy (IST), including anti-thymocyte globulin (ATG) combined with cyclosporine A (CsA) [3], as well as to cyclophosphamide (CY) [4], supports this concept.

The rationale for the administration of IST to SAA patients without hematopoietic stem cell allografting then relies on the evidence that a hyperactivated immune system drives auto reactive T-cell clones to destroy the individual’s own stem and hematoprogenitor cells in the bone marrow [1,2].

A response rate up to 80% [5], with a five-year survival of 75% to 93% for SAA patients immunosuppressed with ATG plus CsA, and granulocyte-colony stimulating factor (G-CSF), has been reported [5,6]. Aplastic anemia patients however, can have a partial response, fail to respond, relapse, or remain dependent of CsA. Despite these drawbacks, the combination of ATG plus CsA is currently recommended as the treatment of choice for SAA patients without an HLA-matched stem cell donor [7].

Immunosuppressive treatment of SAA with ATG and CsA has been associated with late clonal disorders, including acute myelogenous leukemia and myelodysplastic syndromes [8]. Cyclophosphamide has also been successfully employed in the treatment of SAA patients, mostly in adults, with no such late clonal disorders ensuing after a follow up of ten years [4]. Due to its profound and long-lasting immunoablative proprieties, CY-based therapy for SAA has been challenged, with a randomized study terminated early due to unexpected high mortality in the CY/CsA treated group [9]; other researchers, however, found no early mortality, but a 65% probability of complete remission at 50 months [10].

We report the long-term follow-up of five children with SAA and no stem cell donor available, treated with HDCY as the only immunosuppressive drug, twelve years after their treatment with high-dose CY [11].

Materials and Methods

The guidelines established in the Helsinki declaration were followed. Written informed consent was obtained from both parents. The Ethics

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and Human Research Committees at our institution approved the protocol for the study.

Five children lacking an HLA-matched stem cell donor and meeting the criteria for the diagnosis of SAA [12] were included in this study.

Paroxysmal nocturnal hemoglobinuria, myelodysplastic syndromes, viral infections, and other causes of pancytopenia were ruled out; cytogenetic studies did not discover any abnormalities.

Due to the fact that ATG was neither produced nor available in Mexico at the time, none of the patients received ATG/CsA therapy. The median time between the diagnosis of SAA and the referral to our center was 11 months; initial bone marrow cell content was <10.0%.

Cyclophosphamide, at a total dose of 200 mg/Kg, was administered once or for one month at 50 mg/kg/day, through a Hickman catheter, without complications. Subcutaneous G-CSF was injected at 5 μg/kg/day, beginning the day after the last CY infusion, a Hickman catheter, without complications. Subcutaneous G-CSF was injected at 5 μg/kg/day, beginning the day after the last CY infusion.

Prophylactic support included norfloxacin, 400 mg/day, acyclovir, 1000 mg/day, and fluconazole, 6 mg/Kg/day.

Follow-up took place monthly during the first year, then each three to six months and once a year after five years of treatment. A bone marrow aspirate and a trephine biopsy were performed during the last annual evaluation.

Results

Table 1 displays pertinent data of the five patients at diagnosis and current hematological values for the three survivors.

The median number of days to reach an ANC >0.5×10⁹/L and a PC>20×10⁹/L was 55 (range 52-126), and 90 days (range 53-126), respectively. Three of the five children obtained a sustained hematological remission with reconstitution of trilineage hematopoiesis and remained free of transfusion support after their discharge and follow-up. No additional IST was required, and no bleeding or infectious complications have been documented during the ensuing twelve years.

After follow-up periods of 153, 157, and 162 months, none of the three survivors has relapsed or developed malignancies, however the younger patient, treated at five years of age, presented for his annual evaluation with a moderate anemic syndrome and easy bruising, developing pancytopenia and display of changes in the peripheral blood; the subsequent aspirate and trephine biopsy of his bone marrow demonstrated changes typical of myelodysplasia; currently he is being studied as a candidate to receive a bone marrow transplant. Two remaining patients have a normal blood count (Table 1). The bone marrow aspirate and a trephine biopsy of his bone marrow has been shown to have a decreased cellularity, estimated at 60% of the normal bone marrow content.

Two of the children treated with HDCY died. A 13-year-old girl developed rhino cerebral mucormycosis and died, with an ANC of 0.09×10⁹/L, one week after completion of the protocol. She was the only patient in the study with a very severe aplastic anemia. The second, a 16-year-old boy, suffered catastrophic thrombocytopenic bleeding in the basil ganglia of the central nervous system, ninety days after HDCY administration; his PC was 11×10⁹/L. He was the older patient in the group.

Discussion

Hematopoietic stem cell transplantation from bone marrow or peripheral blood is the treatment of choice for SAA patients who have an HLA-identical sibling donor, with survival rates around 90% [8,13]; an actuarial 2-year survival of 73% for matched unrelated HSCT has been reported [14]. Unfortunately, most SAA patients lack an HLA-compatible donor and, in the absence of IST or HSCT, survival is about 24 months [15]. As recently noted, graft rejection, GVHD, and poor immune reconstitution hamper the success of hematopoietic grafting, whereas IST is limited by the lack of a complete sustained response, relapse, and occasionally, clonal evolution [16].

We are familiar with the administration of HDCY used in the conditioning regimens for BMT and, particularly, peripheral blood HSCT for SAA [17], as well as in the utilization of new drug regimens for SAA pre-transplant conditioning [18]; We have also recently reported on the results of treating AA patients with androgens (danazol) as first-line therapy, finding that even with this modified anabolic/immune regulator and the utilization of modern prophylactic antibiotics, antifungals and antivirals plus intense platelet support the results remain similar to those of 40 years ago [19]. Based on these experiences and the lack of ATG in our country at the time, we choose HDCY as a viable option to rescue hematopoiesis in children with SAA without an HLA-compatible stem cell donor.

Cyclophosphamide at the doses employed in this study restored hematopoiesis in three of five children. The treatment was successful despite the long time elapsed between the diagnosis of SAA and the beginning of IST. The two patients with the longest pretreatment evolution, 13 and 18 months, survived, making this form of therapy another option for patients with long-standing disease. The mean 77 days needed to reach an ANC >0.5×10⁹/L in our patients contrasts with the 45 days reported in a study including nineteen adult patients.
although in that study PC recovery took a median 125 days [10], compared with 89 days in ours.

Due to the fact that response is gradual [10], therapy with HD Cy can require a prolonged stay in the hospital and significant support therapy, particularly with G-CSF, habitually requiring several months to reach a complete hematologic response, adding to the whole cost of this form of treatment. For these reasons this form of therapy has not been used frequently, in addition, new approaches to treat AA, including monoclonal antibodies as immunosuppressive agents, which we have recently reviewed [20] although initially more expensive, have considerable less secondary effects and almost no need for hospitalization, although their long-term efficiency has not yet been established.

Outcomes with matched unrelated donor HSCT have improved, due to factors including better donor selection, support therapy, and improved transplant protocols. Results with haploidentical donors and umbilical cord blood stem cells are still being investigated, with suboptimal results, mainly due to high graft rejection rates, GVHD, and infectious complications. Investigation of new IST protocols has not improved outcomes over those offered by administration of ATG and CsA. More recently, the role of biological therapy alternatives, including principally alemtuzumab, in SAA patients has been investigated with some promising results and an oral thrombo mimetic, eltrombopag, is showing good activity in refractory SAA cases [16].

Immunosuppression with HD Cy offers two distinctive advantages over traditional immunosuppressive drugs: the possibility of long-term sustained remissions and independence of the immunosuppressor after recovery. Both of these advantages are infrequent after administration of ATG/CsA-based regimens, as both, adults and children treated with these drugs can suffer relapses, partial responses, drug-dependency or late clonal hematologic disorders [1,5,21]. An update after 38 months of follow up on twenty one SAA patients included in a truncated study [9], found relapses on 6/13(46%) patients treated with ATG/CsA, compared with 2/8 (25%) of those receiving HD Cy/CsA [22]. However, a recent update on the 10-year follow-up of 67 patients treated with HD Cy found a response rate of 71%, actuarial event-free survival was 58% in 44 treatment naive SAA patients; at 10 years, overall actuarial survival, response, and actuarial event-free survival rates were 62%, 48%, and 27%, respectively [23]. High-dose cyclophosphamide is highly effective therapy for severe aplastic anemia.

No relapse occurred in our three surviving patients and only during the last year of vigilance one of them developed anemic syndrome and peripheral blood morphology abnormalities later confirmed to reflect the mielodysplasia in his bone marrow. In retrospective analysis, this patient was the younger of the five children initially treated with HD Cy/G-CSF; he also required the most intense packed red blood cell and platelet concentrates support, endured the longest post-HD Cy hospital stay days and also required more days to reach acceptable ANC and PLT counts, remaining with the lower values on the CBC along the following twelve years

The other two patients have not late clonal blood disorders developed after twelve years of close observation.

Remarkably, HD Cy has been administered as salvage therapy for SAA patients who do not have an HLA-matched donor and who also failed to respond to conventional ATG/CsA therapy, with 9/17 (53%) patients on drug-free remission at a median follow up of 29 months [24]; median time to ANC recovery in this group was 54 days, whereas platelet recovery took 99 days, similar to 55 and 90 days observed in our patients.

It is important to note that after twelve years of therapy with HD Cy and G-CSF the morphological analysis of the bone marrow aspirate revealed myelodysplasia in one of our patients, with no evidence of bone marrow dysplasia in the other two patients, although the histopathology of the biopsies revealed normal morphology but with considerably reduced cellularity, which had no repercussion, other, clinical or in the values of the complete blood count, that remained within the normal range, in consequence we can conclude that, quantitatively, the repopulation of the aplastic bone marrow after HD Cy, although enough in these two patients to lead a normal life in the long term, is partial.

In conclusion, as other immunosuppressive protocols have not improved ATG/CsA results, intensive single-agent immunosuppression with HD Cy backed with G-CSF therapy can represent a third-line treatment for children suffering from SAA who do not have an HLA-compatible related or unrelated donor, and for those who fail to respond to or do not have access to ATG/CsA or the newest monoclonal antibodies currently being studied. Long-standing disease does not appear to represent an obstacle for this treatment modality, which can restore normal or near-normal trilineage hematopoiesis and represents an additional opportunity for obtaining a durable complete remission with a good long-term quality of life.

References


