Tzu Chi Medical Journal 23 (2011) 100–102

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Case Report

Successful allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning in a patient with severe aplastic anemia and active infection

Tso-Fu Wang [a,b], Yi-Feng Wu [a], Yu-Huai Ho [c], Shih-Che Huang [b,d], Sung-Chao Chu [a], Ruey-Ho Kao [a,b,*]

[a] Department of Hematology and Oncology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[b] Department of Medicine, College of Medicine, Tzu Chi University, Hualien, Taiwan
[c] Department of Infection, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[d] Department of Gastroenterology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 11 January 2011
Received in revised form
16 February 2011
Accepted 2 March 2011

Key words:
Hematopoietic stem cell transplantation
Infection
Reduced intensity conditioning
Severe aplastic anemia

ABSTRACT

Infection is the major cause of mortality in patients with severe aplastic anemia (SAA) and often results in postponement of immunotherapy or transplantation treatment. We report on a 23-year-old man with very SAA with almost no neutrophils who was primarily treated with peripheral blood stem cell transplantation from an HLA-identical sibling. He received reduced dose conditioning with cyclophosphamide and antithymocyte globulin during active infection with typhlitis and pneumonia. Cyclophosphamide 50 mg/kg/d was given on Day 4 and Day 3 before transplantation and antithymocyte globulin Fresenius 20 mg/kg/d was given on Day 3 and Day 2. Neutrophils and platelets were engrafted on Day +18 and Day +20 after transplantation. Symptoms and signs of acute or chronic graft versus host disease were not observed as of Day +545 after transplantation. Allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning may be considered as the primary therapy for SAA complicated by severe infection.

1. Introduction

Severe aplastic anemia (SAA) is characterized by a failure of blood cell production with a marked hypocellular bone marrow resulting in cytopenia. Because neutropenia is inevitably present in patients with SAA, infections are the major cause of morbidity and mortality in these patients. Hematopoietic stem cell transplantation (HSCT) is the curative approach for patients with SAA but adequate infection control before the transplantation is recommended. In this report, we successfully completed allogeneic peripheral blood stem cell transplantation (PBSCT) as the first-line therapy in a patient with very SAA with almost no neutrophils during active infection with typhlitis and pneumonia.

2. Case report

A 23-year-old man presented with fever, hypotension, diffuse petechiae, abdominal pain, hematuria, and tarry stools in 2007. He was admitted to the intensive care unit under the impression of septic shock and gastrointestinal bleeding. His hemogram showed white blood cells $0.34 \times 10^3/\mu L$, neutrophils 0%, hemoglobin 9.4 g/dL, and platelets $5 \times 10^3/\mu L$.

Abdominal computed tomography (CT) disclosed marked intramural edema and mucosal wall thickening of the cecum and terminal ileum indicating an active infectious process in the right lower quadrant (RLQ) of the abdominal bowel loops. Typhlitis with regional peritonitis was impressed. Two sets of blood cultures revealed growth of *Klebsiella pneumoniae*.

Bone marrow aspiration and biopsy examination performed for pancytopenia prolonged more than 2 weeks and both showed marked hypocellularity (<10%). Identifiable causes of pancytopenia were ruled out and he was diagnosed with very SAA. Although the tarry stools improved after blood transfusion and supportive care, the intermittent spiking fever up to 39.5°C and abdominal pain remained despite use of granulocyte colony-stimulating factor

* Corresponding author. Department of Hematology and Oncology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 856 1825x2228; fax: +886 3 857 7161.
E-mail address: rueyhokao@tzuchi.com.tw (R.-H. Kao).

1016-3190/$ – see front matter
doi:10.1016/j.tcmj.2011.03.006

(G-CSF) and strong antibiotics (meropenem, gentamycin, teicoplanin, and fluconazole) for 3 weeks. A gallium-67 scan to assess inflammatory activity showed a focal area of increased uptake of radioactivity in the right lower abdominal region in the peritoneum on single photon emission CT images (Fig. 1A) His condition became stable after changing the antibiotics to tigecycline, ceftazidime, and micafungin, but a low-grade fever around 38°C remained. An abdominal CT scan showed a persistent lesion in the RLQ of the abdomen (Fig. 1B), and a newly developed active infection was visible in the right lower lung. The spiking fever occurred again the following week and chest radiography showed the patches had progressed over the right upper and lower lung. A serologic test, sputum analysis, and bronchoaveolar lavage yielded negative results for pathogens, such as bacteria, Mycoplasma, *Pneumocystis carinii*, Legionella, and cytomegalovirus. About 7 weeks after admission, empirical treatment with amphotericin B with dose escalation to 1 mg/kg was added to the broad-spectrum antibiotics for the persistent spiking fever. Chest radiography showed slightly improving lung patches (Fig. 1C) but the intermittent fever remained. His white blood cells count was still less than 500/μL with almost no neutrophils (0–2%), which did not improve with G-CSF therapy. Blood transfusions were required more than twice per week to maintain his hemoglobin level higher than 8 g/dL and platelet level greater than 20×10^3/μL.

The patient's 21-year-old human leukocyte antigen-identical sister agreed to donate stem cells. The donor's stem cells were was mobilized with 10 μg/kg/d recombinant human G-CSF daily for 5 days by subcutaneous injection. Peripheral blood stem cells were collected on the 5th day by continuous flow blood cell apheresis. The patient was transferred to the transplantation ward on the 51st day of hospitalization and received conditioning with cyclophosphamide (Cy) 50 mg/kg/d on Day 4 and Day 3 before transplantation and antithymocyte globulin (ATG Fresenius) 20 mg/kg/d on Day 3 and Day 2. The donor's unmanipulated stem cells were infused, containing 8.6×10^6 CD34$^+$ cells/kg of the patient's weight. Cyclosporin A (CsA) and short-term methotrexate were administered as graft-versus-host disease (GVHD) prophylaxis. CsA was administered from 1 day before transplantation and adjusted according to blood levels (300–400 ng/mL). Methotrexate was injected intravenously at a dose of 15 mg/m^2 on Day +1 after transplantation and 10 mg/m^2 on Day +3, Day +6, and Day +11 after transplantation. The patient received 300 μg G-CSF per day from 1 day after transplantation until

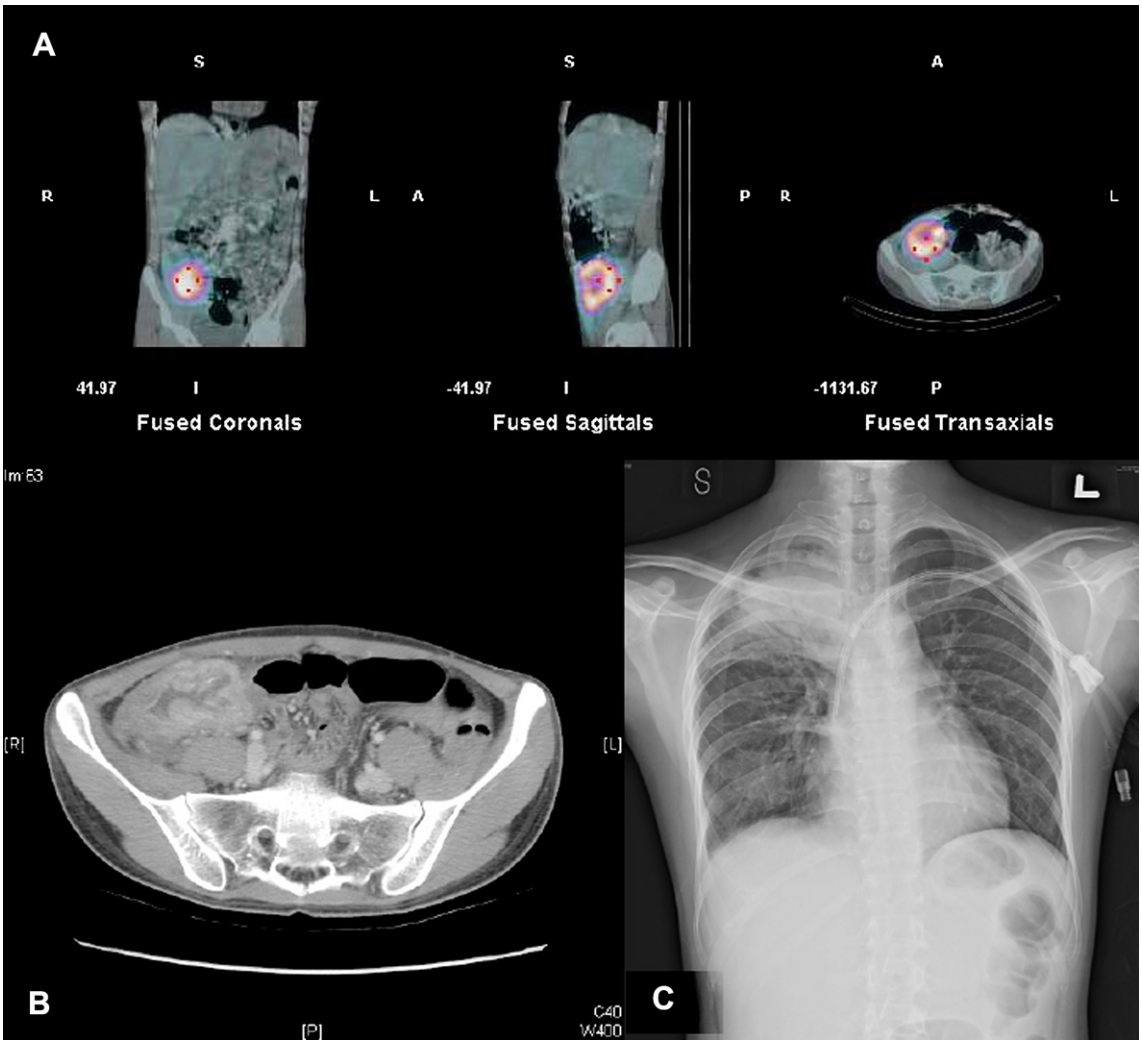

Fig. 1. (A) Gallium-67 scan for inflammatory activity reveals a focal area of increased uptake of radioactivity in the right lower abdominal region, which is suspected to be regional peritonitis (SPECT/CT images). (B) Pelvic CT with contrast medium administration shows marked cecal wall thickening with pericolonic inflammatory stranding. (C) Chest radiography reveals patchy infiltrations in the right upper and lower lung fields. An air bronchogram is also noted in the upper lung field. CT = computed tomography; SPECT = single photon emission computed tomography.

the absolute neutrophil count reached $0.5 \times 10^3/\mu L$ on Day +18 after stem cell infusion. The platelet count was maintained above $30 \times 10^3/\mu L$ with platelet transfusions on Day +20. Fever subsided after Day +11 of transplantation. An abdominal CT scan on Day +16 after transplantation showed persistent but resolving lesions in the RLQ of the abdomen. The hospitalization course after transplantation was smooth and donor origin engraftment was confirmed by polymerase chain reaction analysis of DNA short tandem repeats. CT-guided biopsy of the right upper lung lesion was performed after full recovery of platelets and revealed aspergillosis infection. The amphotericin B was discontinued at an accumulated dose of 2 g and therapy was shifted to oral voriconazole after discharge.

CsA was then tapered and discontinued 6 months after transplantation because there was no evidence of GVHD. No symptoms or signs of chronic GVHD were noted at the latest follow-up at the outpatient clinic as of Day +545 after transplantation.

3. Discussion

SAA occasionally presents with life-threatening infection at diagnosis but seldom can be treated with transplantation during active infection. Bacterial and fungal infections are common causes of morbidity and mortality in patients with SAA [1,2]. In patients with active infections, broad-spectrum antibacterial and/or antifungal agents are usually given to completely resolve the infection before allogeneic HSCT is planned. Many patients succumb to infections before HSCT and most of them die of sepsis from pulmonary or abdominal infection. In those patients with infections who do undergo HSCT, the outcome is generally poor because of infection-related mortality and an increased incidence of graft rejection [3,4]. Although active fungal infection is not an absolute contraindication for transplantation, the early mortality rate is 22–27% for patients with active fungal infection receiving HSCT [5,6]. In this report, the patient successfully received allogeneic HSCT as first-line treatment of SAA during active infection with typhlitis and pneumonia.

Because graft failure depends on residual host immunity, an intense conditioning regimen for SAA patients undergoing transplantation was previously thought to be important. This was initially accomplished through the addition of total body irradiation to conditioning chemotherapy. Conditioning regimens with radiation indeed resulted in lower rates of graft failure [7] but were also associated with significant early and late toxicities [4,8,9]. The necessity for total body irradiation was questioned after the introduction of ATG in the conditioning regimen [10–12]. The use of thoracoabdominal irradiation in combination with Cy was associated with higher acute and chronic GVHD rates and lower overall survival, compared with that seen with Cy and ATG [13]. Therefore, Cy plus ATG is the current standard for transplantation conditioning for SAA [14]. Accumulating evidence from fludarabine-containing conditioning regimens also shows that engraftment does not absolutely depend on the intensity of the cytotoxic drugs in conditioning [15,16]. However, in one study, clinically significant toxicity still occurred in conditioning in 21% of patients with 6.9% mortality [17]. The United State Food and Drug Administration has not yet approved fludarabine for use in conditioning chemotherapy in transplantation in patients with SAA or acute leukemia. In our patient, we reduced the Cy dose to half of the conventional myeloablative-conditioning regimen in combination with a two-thirds dose of ATG to avoid severe toxicity and used PBSCT for potential faster engraftment. Although a number of studies have shown that PBSCT is associated with a higher risk of chronic GVHD, acute/chronic GVHD and overall mortality with bone marrow and PBSC were comparable in patients older than 20 years [18]. This patient had no major toxicity and survived severe neutropenia with active infection. Fortunately, there were no signs or symptoms of GVHD at the latest follow-up.

In conclusion, we report our experience with a patient with newly diagnosed very SAA with almost no neutrophils who was successfully treated with reduced intensity conditioning PBSCT as the first-line therapy during active infection. This suggests that primary allogeneic PBSCT with a dose-reduced conditioning regimen is safe and effective in the treatment of SAA with active infection.

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