Successful Treatment of Primary Plasma Cell Leukaemia by Allogeneic Stem Cell Transplantation from Haploidentical Sibling

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Primary plasma cell leukaemia (PCL) is a rare, aggressive neoplasm of plasma cell dyscrasia. Conventional chemotherapy is usually ineffective, with an overall survival of only 8 months. Here, we describe a 42-year-old man with primary PCL, who was successfully treated with haploidentical (2-HLA loci mismatched) haematopoietic stem-cell transplantation (HSCT). To overcome the human leukocyte antigen (HLA) disparity, in vivo T-cell purging by the pre-transplant administration of antithymocyte globulin followed by a conventional prophylactic treatment against graft-versus-host disease (GVHD) resulted in an avoidance of severe GVHD as well as infectious complications. The patient has maintained complete remission for 13 months after haploidentical HSCT, indicating that a graft-versus-PCL effect might be preserved. Haploidentical HSCT can be a potentially curative treatment for patients with primary PCL who do not have an HLA-identical donor.

Key words: plasma cell leukaemia – haploidentical – stem cell transplantation – ATG

INTRODUCTION

Primary plasma cell leukaemia (PCL) is a very rare, aggressive variant of multiple myeloma (MM) accounting for 2–3% of all plasma cell dyscrasias (1). It is defined as malignant proliferation first diagnosed in the leukaemic phase without preceding MM. Patients with this entity usually have clinical presentations in advanced stages and multiple organ insufficiency due to the involvement of PCL at greater levels than MM. They then usually have a fulminating course and poor prognosis (1–4).

Treatment with standard alkylating agents and steroids is poorly effective (median survival 2 months) (5,6), although a combination of chemotherapy such as VAD chemotherapy, M-80 protocol or hyper-CVAD regimen might provided slight better but not yet promising results (4,7). Recently, several preliminarily reports have demonstrated that high-dose chemotherapy followed by allogeneic haematopoietic stem-cell transplantation (HSCT) resulted in the sustained long-term survival of eligible patients (8), suggesting the possible effect of graft-versus-PCL as shown for MM (9,10). In this report, we describe the first case of a chemotherapy-resistant primary PCL, which was successfully treated with allogeneic HSCT from a haploidentical (2-HLA loci mismatched) sibling donor. In vivo T-cell depletion by antithymocyte globulin (ATG) contained in the conditioning regimen might avoid the development of severe graft-versus-host disease (GVHD), whereas a graft-versus-PCL effect still might be preserved (11) in this case. Considering the aggressive nature of this disease, haploidentical HSCT can be a treatment option based on graft-versus-PCL effects in addition to intensive conditioning regimens for patients with primary PCL who do not have an HLA-identical donor.

CASE REPORT

A 42-year-old man was referred to our hospital because of leukocytosis and acute renal failure in May 2006. On admission, he manifested high fever and severe diarrhoea;
however, spleen, liver and lymph nodes were not palpable. Endoscopic colonoscopy and histological findings of colon revealed a mild chronic inflammation. Haemoglobin concentration was 15.5 g/dl, the platelet count 103 × 10^9/l and the white blood cell (WBC) count 53.3 × 10^9/l with 55% abnormal cells. The serum level of total protein was 8.0 g/dl, and the serum level of creatinine and blood urea nitrogen increased up to 8.71 mg/dl and 84 mg/dl, respectively. The serum level of IgG, M, A, D and E was 2244 mg/dl, 1411 mg/dl, 550 mg/dl, 2.5 mg/dl and 1135 IU/ml, respectively. A bone marrow aspirate was hypercellular with 54% abnormal plasma cells, which were positive for IgM, CD138, CD19, CD30, CD35 and CD38, but negative for CD20, CD34 and CD56. Bone marrow smear showed abnormal plasma cells with classic eccentric nuclei, prominent paranuclear hof and abundant basophilic cytoplasm. Cytogenetic analysis of bone marrow showed normal in all metaphase cells. Radiological studies such as computed tomography and scintigraphy demonstrated that the patient had no extramedullary masses and bone lesion. Serum and urinary protein electrophoresis revealed no monoclonal protein, indicating that these myeloma cells were categorized as non-secretary type. On the basis of these findings, a diagnosis of primary PCL was made. Acute renal failure was considered due to dehydration and PCL. The patient was also found to be positive for hepatitis B virus (HBV) surface antigen and envelope antigen, and his serum HBV-DNA level was 3.8 log of the genome equivalent per millilitre. Therefore, he was also diagnosed as an HBV carrier.

On the day of admission, the patient received a VAD regimen consisting of vincristine 0.4 mg and doxorubicin 10 mg/m^2 on days 1–4, and dexamethasone 40 mg on days 1–4 and 13–16. Concurrently, to prevent the reactivation of HBV, treatment with lamivudine (100 mg daily) was started. Diarrhoea and high fever were gradually improved and resolved by day 10. On day 14, WBC count and serum creatinine level returned to normal levels. However, on day 17, the patient developed high fever again, and WBC count increased to 13.12 × 10^9/l with 24% of leukaemia cells. Therefore, the patient received chemotherapy according to the hyper-CVAD regimen, comprising cyclophosphamide 300 mg/m^2 every 12 h for days 1–3, doxorubicin 50 mg/m^2 on day 4, vincristine 2 mg on days 4 and 11 and dexamethasone 40 mg on days 1–4. Nine days after treatment with hyper-CVAD regimen, a WBC count was normalized to 4.7 × 10^9/l without leukaemia cells. On day 12, however, leukaemia cells appeared again in the peripheral blood, and the patient successively underwent intensive treatment with cytosine arabinoside 2.0 g/m^2 every 12 h on days 1–5 and mitoxantrone 10 mg/m^2 on days 1 and 2, and he achieved complete remission (CR) that was evaluated by flow cytometry. Then, he was administered interferon alpha (six million units) three times per week (12) as a post-remission therapy.

Since the patient presented with rapid clinical course due to the aggressiveness of the disease, we decided to perform allogeneic HSCT. However, the patient had no HLA-identical donor among his family or the Japan Marrow Donor Program, and there was no appropriate umbilical cord blood with sufficient CD34⁺ cell doses for HSCT in the Japan Cord Blood Bank Network. In addition, his disease status did not allow us to search or wait for appropriate donors. Therefore, we selected his sister who had haplo-type-identical, two loci-mismatch HLA phenotype (A and DR loci) as an alternative donor. The patient’s HLA phenotype was A1101, A2402, B1501, B5401, DR0901 and DR1405, and that of the donor was A2602, A12402, B1501, B5401, DR1406 and DR1405. She was not a non-inherited maternal antigen (NIMA) mismatched donor according to microchimerism analysis. Written informed consent for this therapy was obtained.

On August 2006, the patient underwent allogeneic peripheral blood stem-cell transplantation (PBSCT) from his sister with HLA mismatched at two loci at CR state (Fig. 1). Unmanipulated PBSCs (CD34⁺ cells, 3.68 × 10^6/kg) were infused after a conditioning regimen including total body irradiation (TBI, 12 Gy), cyclophosphamide (120 mg/kg) and rabbit ATG (Nippon Zoki Pharmaceutical Co. Ltd) 1.5 mg/kg on days −5 to −2. Acute GVHD prophylaxis comprised methotrexate (10 mg/m^2 on day 1, 7 mg/m^2 on days 3 and 6) and tacrolimus (0.03 mg/kg). Engraftment was documented on day 14 after allogeneic PBSCT, confirmed by complete donor chimerism using short tandem repeat-based polymerase chain reaction assay. On day 12, grade II acute GVHD developed, confined to the skin; this responded to methylprednisolone (mPSL, at a dose of 2 mg/kg daily), which was then gradually tapered to a maintenance dose of PSL 10 mg daily (Fig. 1).

On day 14, cytomegalovirus (CMV) antigenemia was detected (10 CMV-positive cells out of 57 900 cells), and pre-emptive treatment with ganciclovir (10 mg/kg daily) was started (Fig. 1). Flow cytometric analysis of peripheral blood on day 41 demonstrated that CD4⁺ and CD8⁺ cells comprised 20.2% (92/µl) and 65.1% (295/µl) mononuclear cells, indicating the severe cellular immunocompromised state of the patient.

![Figure 1](image.png)

**Figure 1.** Clinical course of the patient. *Number of CMV-positive cells detected out of 70 000 leukocytes. **Serial change in numbers of CD4⁺ and CD8⁺ T cells after haploidentical HSCT. TBI, total body irradiation; ATG, antithymocyte globulin; GVHD, graft-versus-host disease; PBSCT, peripheral blood stem-cell transplantation; CMV, cytomegalovirus.
They deliberated that a megadose of highly purified stem cells might be crucial for promoting engraftment across the histocompatibility barrier as well as avoidance of severe GVHD. In contrast, other approaches using intensification of GVHD prophylaxis or potent pre-transplant immune suppression with ATG (18,19) or alemtuzumab (20) have described similarly favourable engraftment rates and protection from GVHD, if unmanipulated grafts were transplanted. All these methods are still experimental and there is no ‘gold standard’ in GVHD prophylaxis. Practically, ex vivo manipulation methods sometimes require commercially unavailable antibody and special devices, and are expensive. Thus, considering availability in our case, an ATG-containing myeloablative regimen was chosen to deplete T cells in vivo and overcome two-loci mismatched disparity.

Haploidentical HSCT has another disadvantage of delayed and incomplete immune reconstitution, resulting in the high incidence of severe infectious complications, especially viral infections (15). In this case, CD4+ and CD8+ T cells were strongly suppressed throughout the patient’s clinical course after HSCT; CMV reactivation was first documented even on day 14 and CMV antigenemia continued to be detectable for 6 months despite treatment with ganciclovir. On the other hand, as an advantage of haploidentical HSCT, the more potent graft-versus-tumour effect would be expected through the histocompatibility disparity (15). In fact, the curative potential of allografts relies on an immune attack of donor cells against MM (9,10), although TBI also could confer durable cytoreductive responses. Moreover, Mohty et al. have disclosed that the potent immunosuppression with ATG as a conditioning regimen did not impair the graft-versus-myeloma effect (11). In this context, haploidentical HSCT can be a treatment option for patients with primary PCL who have poor prognoses and no HLA-identical donor.

In conclusion, we describe the first case with primary PCL to be successfully treated, to our knowledge, with haploidentical (2-HLA loci mismatched) HSCT after potent pre-transplant immune suppression with an ATG-containing myeloablative regimen. Given the aggressiveness of this disease, allogeneic HSCT is a potentially curative therapy for patients with primary PCL based on graft-versus-PCL effects in addition to intensive conditioning regimens.

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Conflict of interest statement
None declared.

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