Complete Hematologic Response and Cytogenetic Remission after Imatinib and Dexamethasone Treatment of a Ph+ Precursor B-cell Acute Lymphoblastic Leukemia in Renal Transplantation Patient

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In this report, we present a case of a patient with Philadelphia chromosome-positive (Ph+) B-cell acute lymphoblastic leukemia after renal transplantation. The patient, a 65-year-old man, had received a kidney transplantation 20 years prior to diagnosis with Ph+ precursor B-cell ALL. Because he was refractory to intensive chemotherapy and had refused to receive additional intensive chemotherapy, he was treated with imatinib and dexamethasone. While this patient experienced a complete hematologic and cytogenetic response, he did not show a complete molecular remission. Eighty days after imatinib combination therapy, the patient relapsed and died from intracerebral hemorrhage. ***(Korean J Hematol 2009;44:62-66.)***

Key Words: Renal transplantation, Philadelphia chromosome, Acute lymphoblastic leukemia, Imatinib

INTRODUCTION

Long-term complications of renal transplantation are increasing in importance as short-term patient and graft survival have improved. Secondary malignancies are well-known long-term complications after a solid organ transplantation.[1)] Skin cancer is the most common malignancy, followed by posttransplantation lymphoproliferative disorder (PTLD).[2)] The majority of PTLDs are classified as non-Hodgkin lymphoma (NHL) but lymphoproliferations such as Hodgkin disease (HD), myeloma or lymphoid leukemia (LL) may also arise after kidney transplantation.[3)] Acute leukemia following organ transplantation is a rare event.

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) accounts for at least 20% of adult cases. Patients tend to be older and have a higher WBC count. Ph+ ALL is associated with a very poor prognosis. Treating Ph+ ALL patients with conventional chemotherapy does not result in a substantial improvement.[4)] Here, we present a patient who developed Ph+ pre-B-cell ALL after renal transplantation and achieved a complete remission after being treated with imatinib and dexamethasone. This is the

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first patient who was diagnosed with Ph+ pre-B-cell ALL after renal transplantation in Korea.

CASE REPORT

The 65-year-old male patient had a history of chronic renal failure requiring hemodialysis at the age of 46. Six months after beginning dialysis, he underwent a living-unrelated renal transplantation and was started on immunosuppressive agents including cyclosporine-A, azathioprine and prednisolone. The immunosuppressive agents were changed to mycophenolate mofetil and cyclosporine-A in July 2006. Nineteen days after renal transplantation, the patient was treated with 6 days of OKT3 bolus therapy because of acute rejection. On a routine follow-up in July 2007, leukocytosis and blasts were observed in a peripheral blood smear.

On admission, splenomegaly was observed during physical examination. Laboratory studies revealed the following: blood urea nitrogen 23mg/dL, serum creatinine 1.0mg/dL, hemoglobin 11.5 g/dL, white blood cell count 96.9×10^9/L, platelet count 195×10^9/L and 83% blast in a peripheral blood smear. A bone marrow aspiration smear and biopsy revealed 91% lymphoblast infiltration (Fig. 1). Immunophenotyping of bone marrow blasts showed positive Periodic acid Schiff (PAS) and negative myeloperoxidase reaction. Flow cytometric analysis showed that the blasts were positive for CD13, CD19, CD33, CD34 and CD45 antigens, and negative for CD10 and CD20. BCR/ABL gene rearrangement was determined 44.8% by fluorescence *in situ* hybridization (FISH) and positive at e1a2 by reverse transcription-polymerase chain reaction (RT-PCR) (Fig. 2). 11q23 gene rearrangement or TEL/AML gene rearrangement was not detected. Pretransplantation EBV serologic status was not docu-

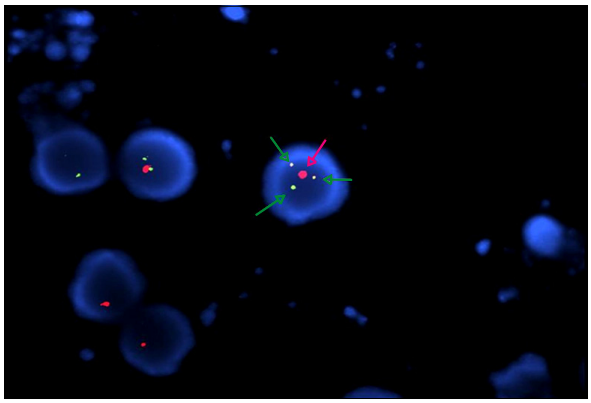

Fig. 2. BCR/ABL gene rearrangement by fluorescence *in situ* hybridization (FISH). Nucleus containing t(9:22) has a native ABL (red arrow), a native BCL (green arrow) and two fusion signal (white arrow). This finding show minor breakpoint signal.

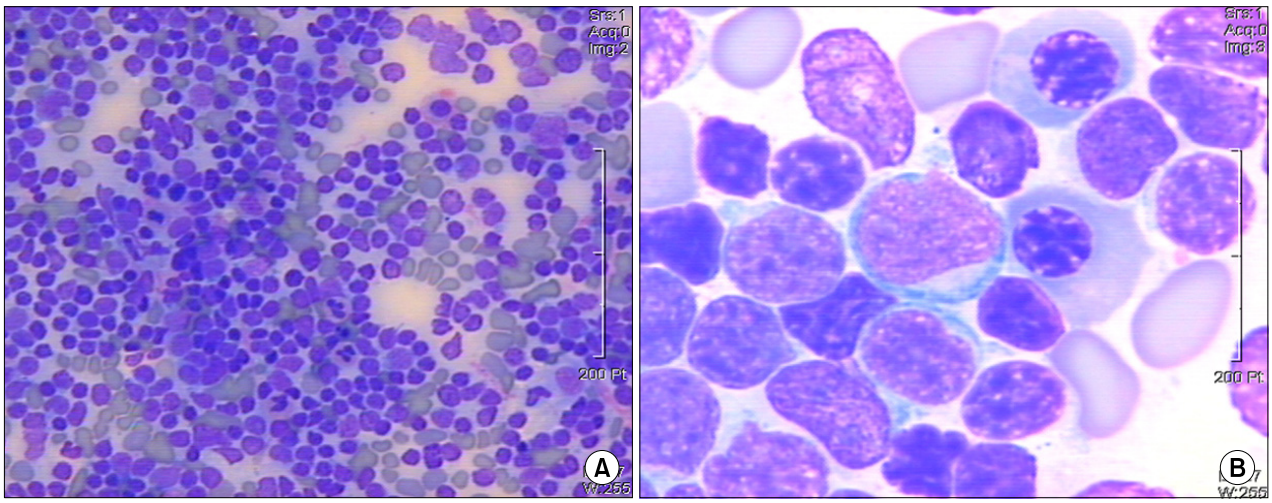

Fig. 1. A bone marrow aspiration examination. (A) *Wright-Giemsa stain, 200*×, there is a diffuse lymphoblast infiltration. It has monotonous small and round nucleus, (B) *1,000*×, blast shows scanty and bluish cytoplasm.

mented, but the patient showed EBV IgG seropositivity at that time. He was CMV and hepatitis C seronegative.

The patient was diagnosed with Ph+ precursor B-cell ALL, and was started on high doses of cyclophosphamide, vincristine, doxorubicin and dexamethasone in Aug 2007. The immunosuppressive agent only decreased cyclosporine-A. On day 20, a follow-up bone marrow aspiration smear and biopsy revealed 34% lymphoblast infiltration. The patient refused to receive additional intensive chemotherapy, so he was started on dexamethasone at 10mg daily for 5 days and imatinib 400mg daily. Three weeks after the dexamethasone and imatinib treatment, bone marrow aspiration and biopsy revealed 1.3% blast infiltration. The BCR/ABL gene rearrangement was not detected by fluorescence *in situ* hybridization (FISH) but was seen by reverse transcription-polymerase chain reaction (RT-PCR). One month after treatment with dexamethasone and imatinib, the patient's common blood count revealed the following: hemoglobin 10.3g/dL, white blood cell count 4.02×10^9/L and platelet count 190×10^9/L. The patient had achieved a complete hematologic and cytogenetic response, but did not have a complete molecular remssion. Eighty days after imatinib combination therapy, the patient was admitted because of dyspnea and general weakness. At that time, the white blood count was 244.4×10^9/L with 62% immature cells. Bone marrow aspiration confirmed the suspected relapse with 90% blast cells and the patient died from intracerebral hemorrhage on day 4 of hospitalization in Jan 2008.

DISCUSSION

Renal transplantation in patients with end-stage renal disease (ESRD) can improve their survival and quality of life. Despite the benefits of immunosuppressive medications to improve graft function and duration, patients may experience several adverse effects, such as the development of neoplasm. Data on occurrence of malignancy after transplant from the Cincinnati transplant tumor Registry and the Australia-New Zealand Dialysis and transplantation (ANZDATA) Registry clearly show that the overall incidence of cancer in renal transplant recipients is greater than in dialysis patients and in the general population.[1,5] There are several reasons why the reported incidence of cancer is higher. First, immunosuppression allows the uncontrolled proliferation of oncogenic viruses. Second, immunosuppression may inhibit normal tumor surveillance mechanisms, allowing unchecked proliferation of "naturally occurring" neoplastic cells. There is also experimental evidence that cyclosporine has tumor-promoting effects mediated by its role in TGF-β production.[6] Third, factors related to primary renal disease or the ESRD milieu may promote neoplasia. Finally, an ascertainment bias may occur due to assiduous monitoring and reporting of transplant patients. It is believed that the cumulative amount of immunosuppression, rather than a specific drug, is the most important factor increasing the risk of cancer. However, there is evidence that the routine use of calcineurin inhibitors can increase the risk of skin cancers, though they are usually not fatal.[7] The long-term impact of currently employed powerful immunosuppression regimens on cancer incidence is unknown. The goal is to prevent cancers while minimizing immunosuppression.

PTLD is a well recognized complication from solid organ transplantation. The majority of malignant lymphoproliferative disorders that occur following solid organ transplantation are of B-cell origin, most commonly NHL. In a study of data obtained from the United States Renal Data System of 66,159 adult Medicare kidney transplant recipients, malignant lymphoid proliferations were diagnosed in 1,169 patients (1.8%). Of these patients, 70, 14, 11, and 5 percent were diagnosed with NHL, MM, LL, HD, respectively.[3] The infection and transformation of B cells by

EBV is an important step in the pathogenesis of PTLD; transformed B cells undergo proliferation that is initially polyclonal, but a malignant clone may evolve. Early diagnosis and treatment are essential to improve clinical outcome and techniques for monitoring EBV viral load after transplantation are being developed to identify patients at high risk for developing PTLD.

Lymphoblastic leukemia occurred in 0.2% of patients among 66,159 kidney recipients in a study of the data obtained from the United States Renal Data System of 66,159 adult Medicare kidney transplant recipients.[3] Older age, diabetic nephropathy and OKT3 therapy were associated with a risk of lymphoid leukemia. Incidence of leukemia was highest in the transplant period of 1991-1995.

Imatinib mesylate is an oral potent competitive inhibitor of ABL that has the ability to induce hematologic and cytogenetic remissions in chronic-phase chronic myeloid leukemia (CML) and gastrointestinal stromal tumors.[8] Imatinib also has limited activity against blast-phase CML and relapsed Ph+ ALL. Several phase 1 and 2 studies have evaluated imatinib for the treatment of patients with relapsed or refractory Ph+ ALL.[9,10] These studies have reported a complete remission rate of approximately 20%, with 60% of patients achieving remission or clearance of peripheral blood blast. But these results are not long-term, with median times to disease progression and overall survival (OS) rates of 2.2 and 4.9 months, respectively. Interestingly, a favorable outcome of 51% disease-free survival after 1 year has been reported in subsets of patients that underwent allogeneic stem cell transplantation during remission.[11]

The prognostic impact of sensitivity to steroids has been assessed in younger ALL adults by the Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) group and has been shown to be correlated with OS.[12] Two clinical studies that used imatinib as an induction agent in elderly patients with newly diagnosed Ph+ ALL disease suggest that imatinib may be superior to chemotherapy in treating elderly patients.[13,14] Vignetti et al.[13] have reported 30 elderly (>60 years) Ph+ patients with ALL who received imatinib plus steroids in induction and imatinib in consolidation until relapse or death. This study showed that the median survival and the median duration of hematologic response for the 29 patients were 20 months and 8 months, respectively, and suggested that an imatinib-steroid protocol is feasible, highly active and associated with a good quality of life. However, despite initial hematologic or cytologic responses, many patients with Ph+ ALL become refractory to imatinib-based therapy, or they relapse within several months. Unfortunately, once resistance develops, the disease is rapid and aggressive in most patients. Therefore the development of other therapeutics, such as Dasartinib and nilotinib, is necessary. Dasartinib is a multi-targeted kinase inhibitor and has been approved for treatment of imatinib-pretreated Ph+ ALL and CML,[15] and nilotinib is a BCR-ABL-targeted agent that is currently being evaluated in a phase 2 trial.

We report a case of Ph+ precursor B-cell ALL in a renal transplant recipient. This is the first case in Korea. The patient achieved a complete hematologic response with a complete cytogenetic remission after treatment with imatinib and dexamethasone but did not have a complete molecular remssion. Our patient survived 6 months with a remission duration of 2 months, followed by an aggressive course prior to death.

요 약

신장 이식의 장기 생존율이 증가함에 따라 지속적인 면역억제제 투여로 인한 부작용도 늘어나며 대표적인 부작용은 악성 종양의 발생이다. 림프세포 증식성질환은 신이식 후 피부암 다음으로 많이 발생하며, non-Hodgkin Lymphoma가 가장 흔하고 드물게 Hodgkin disease, 다발성 골수종, acute lymphoblastic leukemia (ALL)도 발생한다. 신이식 후에 백혈병 발생은 외국 보고는 있지만

국내 보고는 아직 없었다. 저자들은 20년 전에 신이식을 받은 환자에서 발생한 필라델피아 양성 급성 림프구성 백혈병 환자를 dexamethasone과 imatinib 병합 요법으로 치료한 1예를 보고하고자 한다.

REFERENCES

1) Penn I. Posttransplant malignancies. Transplant Proc 1999;31:1260-2.
2) Saadat A, Einollahi B, Ahmadzad-Asl MA, et al. Posttransplatation lymphoproliferative disorders in renal transplant recipients: report of over 20 years of experience. Transplantation Proc 2007;39:1071-3.
3) Caillard S, Agodoa LY, Bohen EM, Abbott KC. Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: characteristics, risk factors and prognosis. Transplantation 2006;81:888-95.
4) Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.
5) Sheil AG. ANZDATA (Australia and New Zealand Dialysis and Transplant Reistry) The 24th annal report 9: cancer report, 2002 (Accessed at http://www.anzdata.org.au/anzdata/AnzdataReport/24thReport).
6) Hojo M, Morimoto T, Maluccio M, et al. Cyclosporin induces cancer progression by a cell-autonomous mechanism. Nature 1999;397:530-4.
7) McGeown MG, Douglas JF, Middleton D. One thousand renal transplants at Belfast City Hospital: postgraft neoplasia 1968-1999, comparing azathioprine only with cyclosporine-based regimens in a single centre. Clin Transpl 2000;16:193-202.
8) Savage DG, Antman KH. Imatinib mesylate - a new oral targeted therapy. N Engl J Med 2002;346:683-93.
9) Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
10) Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemia. Blood 2002;100:1965-71.
11) Wassmann B, Pfeifer H, Scheuring U, et al. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL). Leukemia 2002;16:2358-65.
12) Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term fellow-up of the GIMEMA ALL 0288 randomized study. Blood 2002;99:863-71.
13) Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-8.
14) Wassmann B, Gökbuget N, Scheuring UJ, et al. A randomized multicenter open label phase II study to determine the safety and efficacy of induction therapy with imatinib (Glivec, formerly STI571) in comparison with standard induction chemotherapy in elderly (>55 years) patients with Philadelphia chromosome-positive (Ph+/BCR-ABL+) acute lymphoblastic leukemia (ALL) (CSTI571ADE 10). Ann Hematol 2003;82:716-20.
15) Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood 2007;110:2309-15.