J Korean Med Sci 2010; 25: 523-6
ISSN 1011-8934
DOI: 10.3346/jkms.2010.25.4.523

Clinical Characteristics of Monomorphic Post-transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoproliferative disorders associated with immunosuppression and Epstein-Barr virus infection. PTLD is classified into three major categories: early lesions, polymorphic PTLD, and monomorphic PTLD. The majority of monomorphic PTLD cases are non-Hodgkin's lymphoma of B-cell origin. This retrospective study was conducted to investigate the incidence, clinical manifestation, treatment, and outcomes of monomorphic PTLD among 5,817 recipients of solid organ or allogeneic hematopoietic stem cell transplantation from five institutions. Fourteen patients with monomorphic PTLD were identified (male:female 11:3; median age 42.6 yr, range 24-60). The overall incidence rate was 0.24%. The most common disease type was diffuse large B cell lymphoma (n=7). The median time between the transplant and diagnosis of PTLD was 85.8 months. However, all cases of PTLD after allogeneic hematopoietic stem cell transplantation occurred within 1 yr after transplantation. Ten of the 14 patients had EBV-positive tumor. Fourteen patients received combination systemic chemotherapy and four patients were treated with radiation therapy. Ten patients achieved a complete response (CR) and two patients a partial response (PR). The median follow-up period for surviving patients was 36.6 months. Nine patients remain alive (eight CR, one PR). Nine of 11 solid organ transplantations preserved graft function. The present study indicates a lower incidence rate and a longer median time before the development of PTLD than those of previous reports. Careful monitoring was needed after allogeneic hematopoietic stem cell transplantation for PTLD.

Key Words : *Monomorphic Post-transplant Lymphoproliferative Disorders*

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Received : 10 May 2009
Accepted : 15 July 2009

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The research was supported in part by the Korean Cancer Study Group.

INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoproliferative disorders associated with the immunosuppression in recipients of solid organ or allogeneic stem cell transplantation. The incidence of PTLD varies from 1% to 20% according to the organ transplanted (1). The Epstein Barr virus (EBV) plays an important role in the pathogenesis of PTLD.

PTLD is typically classified into three major categories: early lesions, polymorphic PTLD, and monomorphic PTLD (2). Monomorphic PTLD is defined by the fulfillment of the criteria for one of the recognized types of lymphoma. The majority of monomorphic PTLD cases is non-Hodgkin's lymphoma of B-cell origin; in contrast, T-cell lymphoma and Hodgkin's disease are rare. The recently updated World Health Organization classification separated classical Hodgkin lymphoma type PTLD from monomorphic PTLD (3).

Although there are several reports on PTLD, there are few data on monomorphic PTLD in Korea. The goal of our study was to investigate the incidence, clinical manifestation, treatment, and outcomes of monomorphic PTLD, including Hodgkin's lymphoma, in Korea.

MATERIALS AND METHODS

This study included all patients who were diagnosed with monomorphic PTLD confirmed by tissue diagnosis among 5,817 recipients of solid organ or allogeneic stem cell transplantation from five institutions in Korea between January 1987 and January 2009. The medical records of these patients

were retrospectively reviewed. The clinical factors evaluated included age, sex, transplanted organ, time from transplantation to diagnosis of PTLD, pathology, EBV status in pathology, tumor stage, performance status, extent of extranodal disease, B symptoms, serum LDH level, graft organ involvement, treatment method, and clinical response to treatment. EBV detection methods included EBV-LMP (latent membrane protein), EBV polymerase chain reaction or Epstein Barr encoded RNA (EBER) in situ hybridization in accordance with the availability in the hospitals. Staging was performed according to the criteria of the Ann Arbor system and the histological subgroups were classified according to WHO classification. This study was approved by the institutional review board of Hanyang University Hospital, Asan Medical Center, Soonchunhyang University Hospital, Busan Paik Hospital, and Pusan National University Hospital.

Overall survival was measured from the date of diagnosis of PTLD to the date of death or last follow-up. Survival curves were estimated using the Kaplan-Meier method.

RESULTS

Patient characteristics

Fourteen patients with monomorphic PTLD were identified from 5,817 transplant recipients. The types of organ transplantation included renal (10 cases, 71.4%), liver (1 case, 7.2%), and allogeneic stem cell (3 cases, 21.4%). The overall incidence rate of monomorphic PTLD was 0.24%. The incidence rates of monomorphic PTLD according to the transplanted organ were 0.35% in kidney (10/2,880), 0.045% in liver (1/2,207), and 0.41% (3/730) in allogeneic stem cell transplantation. Patient characteristics are summarized in Table 1. The study group included 11 men and three women, and the median age at the time of PTLD diagnosis was 42.6 yr (range 24-60). All solid organs were obtained from living donors. The initial diagnosis of three patients who underwent allogeneic stem cell transplantation included 2 cases of aplastic anemia and one case of hemophagocytic syndrome. The median time between the transplant and diagnosis of PTLD was 85.8 months. All cases of PTLD after allogeneic hematopoietic stem cell transplantation occurred within 1 yr after transplantation (early onset PTLD), whereas the majority of PTLD after solid organ transplantation (10/11) occurred after 1 yr (late onset PTLD). The most common disease type was diffuse large B cell lymphoma (50.0%), followed by peripheral T cell lymphoma (28.6%), Hodgkin's disease (14.3%), and one case of anaplastic large cell lymphoma. One patient had involvement of the graft organ and seven (50%) patients had extranodal involvement, most commonly in the liver (n=3). Five patients were classified as stage IV. Nine patients had elevated serum LDH, and ten patients demonstrated EBV positivity in the tumor. In EBV negative cases, two patients were diagnosed as diffuse large B cell lymphoma, one patient diagnosed with peripheral T cell lymphoma, and remaining diagnosed as anaplastic large cell lymphoma. According to the International Prognostic Index, six patients were low risk (42.9%), six patients were low-intermediate risk (42.9%), and two patients were high risk (14.2%).

Table 1. Patient characteristics

No	Age (yr)	Sex	Transplanted organ	Pathology	Time to PTLD (month)	EBV	IPI	Stage	Treatment	Response	Last status (survival duration)
1	41	M	Kidney	HD	116.7	+	0	IIB	ABVD, radiation	CR	CR, alive (46.5 mon)
2	60	M	Kidney	DLBCL	11.4	+	2	IA	R-CHOP, radiation	CR	CR, alive (42.7 mon)
3	42	F	Kidney	DLBCL	95.1	–	0	IIA	CHOP	CR	CR, alive (63.4 mon)
4	33	M	Kidney	DLBCL	90.2	+	2	IVB	CHOP	CR	CR, death (14.7 mon)
5	46	M	Kidney	DLBCL	110.2	+	4	IVA	R-CHOP	PR	Not CR, death (9.2 mon)
6	44	M	Kidney	PTCL	117.2	+	2	IIIA	CHOP	CR	CR, alive (36.6 mon)
7	56	M	Liver	DLBCL	43.5	+	0	IIA	R-CHOP	CR	CR, alive (30.3 mon)
8	37	F	Kidney	PTCL	29.8	+	1	IIA	CHOP	CR	Not CR, death (20.8 mon)
9	25	M	Bone marrow	HD	5.0	+	1	IIA	ABVD, radiation	PR	Not CR, alive (10.5 mon)
10	31	M	Kidney	PTCL	81.4	–	2	IVB	CHOP	PD	Not CR, death (7.3 mon)
11	55	M	Kidney	Anaplastic large cell	182.0	–	0	IA	CHOP, radiation	CR	CR, alive (61.4 mon)
12	24	M	Bone marrow	DLBCL	5.9	+	4	IVB	R-CHOP	Not determined	Not CR, death (1.5 mon)
13	44	F	Bone marrow	DLBCL	5.8	–	2	IVA	R-CHOP	CR	CR, alive (15.5 mon)
14	60	M	Kidney	PTCL	174.7	+	2	IIIA	CHOP	CR	CR, alive (9.9 mon)

PTLD, Post-transplant lymphoproliferative disorders; EBV, Epstein-Barr virus; IPI, international prognostic index; HD, Hodgkin's disease; DLBCL, diffuse large B cell lymphoma; PTLD, peripheral T cell lymphoma; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; R-CHOP, rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; CR, complete response; PR, partial response; PD, progressive disease.

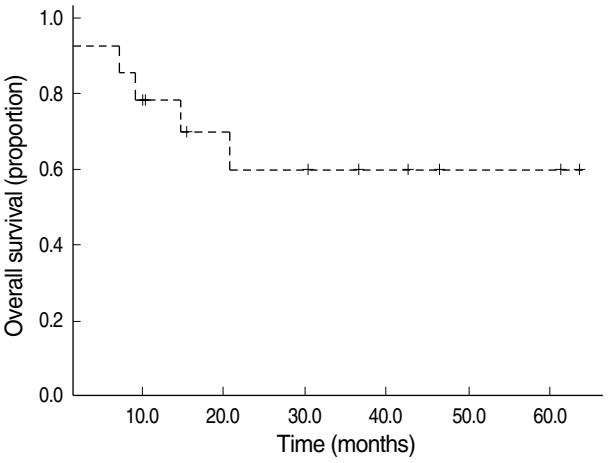

Fig. 1. Overall survival for all patients.

Treatment and outcome

Administration of immunosuppressive agents was reduced in all patients except for one patient who was not receiving immunosuppressive treatment at the time of diagnosis because the grafted organ had already been rejected. Fourteen patients were treated with combination systemic chemotherapy as follows: CHOP (cyclophosphamide, adriamycin, vincristine, prednisone; n=6), R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone; n=5), ABVD (adriamycin, bleomycin, vinblastine, dacarbazine; n=2), and CHOP followed by autologous stem cell transplantation (n=1). Four patients received radiation therapy.

Because one patient died from infection during chemotherapy, 13 patients were assessed for response analysis. The overall response rate was 92.3%; 10 patients achieved complete response (CR) and two achieved partial response (PR). Among the 10 patients who achieved CR, one patient subsequently suffered relapsed diffuse large B cell lymphoma at 11.3 months. For the two patients who achieved PR, one patient diagnosed with Hodgkin's disease was treated with four cycles of ABVD followed by radiation therapy (4,400 cGy) and remained in a state of PR at the time of the last follow up. The other patient diagnosed with diffuse large B cell lymphoma died due to disease progression. Among 11 solid organ transplantations, nine patients preserved graft function.

The median follow-up period for surviving patients was 36.6 months. There were five deaths during follow-up (35.7 %): three due to infection and two due to disease progression. Nine patients were still alive (8 CR, 1 PR) at the time of the last follow-up. The median survival was not reached and 3-yr survival rate was 59.9% (Fig. 1).

DISCUSSION

In this retrospective analysis the incidence rate of monomorphic PTLD was 0.24% and the median time between the transplant and diagnosis of PTLD was 85.8 months. Four out of 14 patients (29%) had EBV-negative PTLD.

The incidence rate of this study was lower than those in previous reports. This might be because our study included only adult monomorphic PTLD patients, and PTLD is more common in children than in adults. In addition, the majority of patients in our study underwent kidney or liver transplantation (5,129/5,817), and the incidence of PTLD is the lowest for recipients of renal or liver allografts and the highest for heart-lung, lung, or intestinal allografts (1, 3). Previous studies on PTLD typically included all PTLD types, from early lesions to monomorphic PTLD, and the incidence of monomorphic PTLD is obviously lower than the overall incidence rate; for example, in one report with an overall incidence rate of 1.2%, the incidence rate of monomorphic PTLD was only 0.48% (4). Finally, since this study was carried out in a retrospective manner, and since patients with only confirmed tissue diagnosis were included in this study, there may be possibilities that some potential candidates may have been left out.

The majority of PTLD occur less than 1 yr after transplantation; however, the median time before the development of PTLD in our study was longer than those in previous reports. PTLD that occurs within 1 yr after transplantation is defined as early PTLD, while that occurs after 1 yr is late PTLD. Early PTLD is commonly EBV-positive, CD20-positive, and involves the graft organ (5). In our study, four patients had early PTLD; three of these were EBV-positive and CD20-positive, and one patient showed graft organ involvement.

Recently, a retrospective study was published which stated the clinical characteristics of PTLD of kidney transplantation in Korea (6). From 2,630 renal transplant recipients, eleven patients were diagnosed with PTLD. Of these, 10 were monomorphic PTLD, and the incidence of monomorphic PTLD was 0.38%. The mean time interval between the time of transplantation and diagnosis of PTLD was 126.6 months. This report also represented low incidence rate and long time interval, which is similar to our results.

Our study revealed that all cases of PTLD after allogeneic hematopoietic stem cell transplantation (HSCT) were early PTLD, whereas the majority of PTLDs after solid organ transplantation (10/11) were late PTLD. Hou et al. reported that the majority of PTLD after allogeneic HSCT occurred within 6 months (7). In their study, the overall mortality rate was 92%, and the major causes of death were disease progression and infection. In addition, pulmonary PTLD showed an aggressive clinical course and poor response to therapy (7). Our study included three patients who received allogeneic HSCT; their time before the development of PTLD was 5.0, 5.8, and 5.9 months, respectively. Of these, one patient had EBV-associated PTLD (diffuse large B cell lymphoma) with pulmonary involvement. Although the patient was treated with R-CHOP, he died from infection 40 days after chemotherapy.

Most cases of PTLD are associated with EBV infection. In the immunosuppressed state, suppression of T-cell activity interferes with immune surveillance and allows the proliferation of latently infected B lymphocytes, and the proliferation of a malignant B cell clone results in lymphoma (8, 9). However, the incidence of EBV-negative PTLD appears to be increasing, and recent reports showed that 20-30% of PTLD cases were EBV-negative. EBV-negative PTLDs occur later than EBV-positive cases, have a higher proportion of monomorphic PTLD, and show a more aggressive clinical course (10, 11). Although the pathogenesis of EBV-negative PTLD remains to be determined, changes in the immunosuppressive regimens and new, unidentified infectious agents might play a role (10). In our study, four cases were EBV-negative; among these, three patients developed PTLD more than 5 yr after transplantation.

Since monomorphic PTLD fulfill the criteria for one of the recognized types of lymphoma, it is difficult to differentiate between monomorphic PTLD and de novo lymphoma in patients who underwent transplantation. It could be a reasonable option to consider monomorphic PTLD if it contains pleomorphism of the transformed cells, variability of cell size, and EBV positive cells (3).

There is no consensus on the best approach to the treatment of PTLD. Reduction of immunosuppressive therapy is the most common initial approach. Other treatment strategies for PTLD included antiviral therapy, systemic chemotherapy, rituximab, interferon α, and radiation therapy (1); however, the treatment outcome and survival of PTLD patients remains poor. In particular, monomorphic PTLD requires more aggressive treatment strategies because of its poor prognosis. In our study, all patients received combination chemotherapy, and the overall response rate was 92.3%. Although this study showed a better response rate than other reports, five of the 14 patients died due to infection or disease progression.

Our study has following limitations: the clinical data were analyzed retrospectively and a relatively small number of patients were included. Nevertheless, our results provide further information on the clinical manifestation, treatment, and outcomes of monomorphic PTLD. Our results showed that a lower incidence rate and a longer median time before the development of PTLD than those of previous reports. However, all cases of PTLD after allogeneic HSCT occurred within 1 yr after transplantation, therefore careful monitoring must be needed in this particular group of patients. Compared with previous reports, our study showed better response rate and survival, and this might be due to the fact that all our patients received combination chemotherapy. In this aspect, we suggest that monomorphic PTLD could lead to a better outcome with an aggressive combination treatment strategies.

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