

Case Report

Small Cell Variant Anaplastic Large Cell Lymphoma: Long-Term Remission after Allogeneic Peripheral Blood Stem Cell Transplant

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Abstract

Anaplastic Large Cell Lymphoma (ALCL) is a peripheral T-cell, non-Hodgkin lymphoma that consists predominantly of large lymphoid cells with expression of CD30 and is often associated with translocations involving the Anaplastic Lymphoma Kinase (ALK) gene. ALK positive (ALK+) ALCL usually presents at a more advanced stage but has a much better prognosis than ALK negative ALCL. One exception is the small cell variant of ALK+ ALCL, which often affects younger individuals, carries a high incidence of leukemic involvement, and has a very poor prognosis. We present a patient with diagnosis of small cell variant ALK+ ALCL who underwent allogeneic stem cell transplantation and has achieved an ongoing disease-free survival of over 9 years after diagnosis. We also review the literature of small cell variant ALK+ ALCL to determine if stem cell transplantation should be considered in patients with this diagnosis.

Keywords: Anaplastic Large Cell Lymphoma; Small Cell Variant of Anaplastic Large Cell Lymphoma; Hematopoietic Stem Cell Transplantation; Allogeneic Bone Marrow Transplantation

Abbreviations

ALCL: Anaplastic Large Cell Lymphoma; ALK: Anaplastic Lymphoma Kinase; ALK+: Anaplastic Lymphoma Kinase Positive; ALK-: Anaplastic Lymphoma Kinase Negative; Allo: Allogeneic; ANC: Absolute Neutrophil Count; APO: Doxorubicin Vincristine Prednisone; Auto: Autologous; BM: Bone Marrow; CHOP: Cyclophosphamide Doxorubicin Vincristine Prednisone; CMV: Cytomegalovirus; CNS: Central Nervous System; COPAD-M: Cyclophosphamide Vincristine Prednisone Doxorubicin Methotrexate; CR: Complete Remission; CSF: Cerebrospinal Fluid; CT: Computed Tomography; D-COMP: Daunomycin Cyclophosphamide Vincristine Methotrexate Prednisone; EBRT: Electron Beam Radiation Therapy; EBV: Epstein-Barr Virus; ECP: Extracorporeal Photopheresis; EFS: Event Free Survival; F: Female; FISH: Fluorescence In Situ Hybridization; GVHD: Graft-Versus-Host Disease; HA: Headache; HBV: Hepatitis B Virus; HD: High-Dose; HIV: Human Immunodeficiency Virus; HLA: Human Leukocyte Antigen; HSCT: Hematopoietic Stem Cell Transplant; HTLV: Human T-Cell Lymphotropic Virus; Hyper-CVAD: Hyperfractionated Cyclophosphamide Vincristine Doxorubicin Dexamethasone; IHC: Immunohistochemical; IT: Intrathecal; LAD: Lymphadenopathy; LDH: Lactate Dehydrogenase; LN: Lymph Node; LUQ: Left Upper Quadrant Of Abdomen; M: Male; MACOP-B: Methotrexate, Doxorubicin Cyclophosphamide Vincristine Prednisone Bleomycin; MIED: High-Dose Methotrexate Ifosfamide Etoposide Dexamethasone; Mo: Months; MTX: Methotrexate; NA: Not Available; NPM: Nucleophosmin; NS: Night Sweats; OS: Overall Survival; PBSCT: Peripheral Blood Stem Cell Transplant; PR: Partial Response; RUQ: Right Upper Quadrant Of Abdomen; TBI: Total Body Irradiation; TPN: Total Parenteral Nutrition; Tx: Therapy; WBC: White Blood Cell.

Introduction

ALCL is a peripheral T-cell, non-Hodgkin lymphoma that is defined by proliferation of predominantly large lymphoid cells with expression of CD30, a cytokine receptor [1]. ALCL consists of three major groups: primary systemic ALK+ ALCL, primary systemic ALK- ALCL, and primary cutaneous ALCL. Approximately 60% of ALCL cases are associated with chromosomal translocations involving ALK [2] on chromosome 2p23, with the most common translocation being t(2;5)(p23;q35), found in 70-80% of cases of ALK+ ALCL [3]. The fusion gene product, NPM-ALK, is a functionally active tyrosine kinase that is associated with malignant transformation of the affected cells [4]. Clinically, patients with ALK+ ALCL have a median age in the thirties and present with more advanced stage, B symptoms, and extranodal involvement than ALK- patients. In contrast, patients with ALK- and primary cutaneous ALCL have a median age in the sixties and present with often a less advanced stage, fewer or no B symptoms, and less extranodal involvement [1,5-8]. Despite advanced presentation, ALK+ ALCL has been shown to have a much better prognosis when compared to ALK- cases, with 5-year overall survival rates of 70% compared to 49% [5]. However, within the ALK+ ALCL group, there are morphological subgroups. While the majority of patients have a good prognosis, the rare small cell variant subgroup has a poor prognosis [9-11].

We present a patient with diagnosis of ALK+ ALCL with small cell variant morphology who underwent allogeneic stem cell transplantation and has achieved an ongoing disease-free survival of 9 years and 8 months after diagnosis. We reviewed the literature of small cell variant subtype of ALK+ ALCL to determine if stem cell transplantation should be considered in patients with this diagnosis.

Case Presentation

In December 2004, a 31-year-old woman presented with three weeks of left upper quadrant pain, severe headache, fevers to 103 °F, chills, and night sweats. Initial physical examination revealed left cervical and right axillary lymphadenopathy with shotty inguinal lymphadenopathy, hepatomegaly 5 cm below the costal margin, and splenomegaly 3 cm below the costal margin. Significant laboratory results on admission included WBC count 35 K/mm³ with 14% atypical lymphocytes, hemoglobin 11.1 g/dL, hematocrit 34.2%, platelet count 329 K/mm³, LDH 214 IU/L, total protein 4.5 g/dL, and albumin 1.7 g/dL. Antinuclear antibody screen was negative along with serologic assays for HIV 1 and 2, HBV, CMV, and HTLV 1 and 2. EBV antibody titers were consistent with a prior exposure but no active infection. Chest, abdomen, and pelvis CT scan with contrast showed scattered abdominal lymphadenopathy, enlargement of liver and spleen with multiple internal low density foci in the spleen, and small bilateral pleural effusions. Lymph node biopsy showed large atypical lymphocytes with prominent nucleoli and IHC stains positive for CD30 and ALK with a subpopulation positive for EMA (Figure 1); flow cytometry revealed CD3 positivity, dim CD5, and a CD4:8 ratio of 55:1. Lymph node cytogenetics showed 5 of 15 metaphases with a 46,XX,t(2;5)(p23;q35) karyotype. Peripheral blood smear showed atypical T-cells with small to intermediate cell size, and cytogenetic examination of a bone marrow aspirate showed 10 of 20 metaphases with the same 46,XX,t(2;5)(p23;q35) karyotype. All studies were consistent with a diagnosis of ALCL, small cell variant, stage IVB.

During initial workup, leukocytosis increased and reached a peak of 69.4 K/mm³ on day 4 of hospitalization. The patient also experienced worsening abdominal pain and hypoxic respiratory failure, eventually requiring intubation. Serial CT scans showed worsening interstitial lung infiltrates. Bronchoalveolar lavage was negative for malignant cells, but pleural fluid analysis showed atypical lymphocytes consistent with a T-cell neoplasm. Patient began therapy with hyper-CVAD [12] with remarkable clearing of pulmonary infiltrates and reduction of hepatosplenomegaly and pain. She was

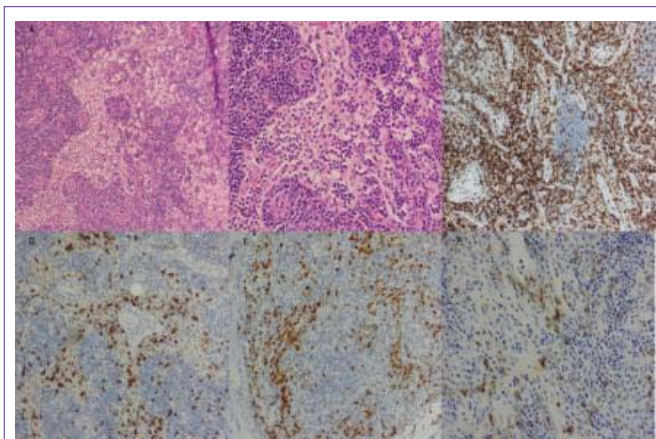


Figure 1: (A) Low power view of lymph node shows dilated nodal sinuses with small cell infiltrate (H&E 10x). (B) Predominant population of small cells with scattered large cells, the latter primarily in the perivascular regions (H&E 20x). (C) CD3 staining shows these cells to be T-cells. Residual follicular structure is evident. (D) CD30 highlights the sinusoidal and perivascular infiltrate. (E and F) The malignant cells are ALK+ with a subpopulation also being EMA+.

able to be extubated on day 12 of hospitalization and discharged on day 23.

The patient completed 2 full courses of hyper-CVAD alternated with high-dose methotrexate and cytarabine (known as courses A and B of hyper-CVAD) including IT methotrexate prophylaxis with good response. Bone marrow biopsies following therapy showed no evidence of ALCL with normal cytogenetics and negative FISH for the t(2;5) translocation. However, the patient developed pustular skin lesions on her upper back and left arm after cycle 2A that showed CD30 and ALK positivity and cellular characteristics consistent with ALCL involvement. These lesions persisted after cycle 2B, and therefore response was classified as PR.

She received allo PBSCT from an HLA-identical sibling in April 2005 with a conditioning regimen of cyclophosphamide 60mg/kg (days -5 and -4) and TBI 12Gy total dose in 6 fractions given twice daily (days -3 through -1). She received methotrexate GVHD prophylaxis on days 1, 3, and 6 along with daily cyclosporine. The patient's hospital course was complicated by mucositis requiring TPN, culture-negative neutropenic fevers, platelet-transfusion-refractory thrombocytopenia, transient non-ischemic cardiomyopathy, and grade 1 acute GVHD of the skin. Platelet count recovered to >20 K/mm³ on transplant day 11 and ANC to >0.5 K/mm³ on day 16. The patient was discharged on day 32 post-transplant with cyclosporine GVHD prophylaxis. As of August 2014, the patient has been in continuous CR for 116 months after diagnosis with a Karnofsky score of 90% as well as all imaging studies, CSF analyses, and bone marrow studies showing no signs of disease.

Discussion

ALCL by Morphological subgroup

There are several morphological subgroups of ALK+ ALCL: the most common classic type, and less common lymphohistiocytic and small cell variants. The classic type comprises about 70% of cases and is characterized histologically by sheets of "hallmark cells," large cells with abundant cytoplasm and a horseshoe-shaped nucleus with multiple nucleoli surrounded by a prominent, pale Golgi region [1,7]. These cells can be found in all ALCL subtypes. The lymphohistiocytic variant comprises 5-10% of cases and is characterized by tumor cells smaller than those in the common type that are often masked by a large number of histiocytes that do not proliferate despite monomorphic appearance. Immunostaining for CD-30 and Ki-67 is particularly important in this variant to identify tumor cells and to distinguish ALCL from malignant histiocytosis [1,7]. The small cell variant of ALK+ ALCL, was first described in 1993 by Kinney, et al. [9] This variant comprises 5-10% of cases, affects primarily younger patients (median age 14 [9]), and is characterized morphologically by a mixture of small, medium, and large lymphoid cells with the nuclei of the small and medium cells often being irregular [1,7]. Interestingly, while the large cells are always CD30+, the small cells are often CD30- [5]. However, in lymph nodes, the small cell variant usually has areas of large CD30+ blasts indicative of the common type of ALCL, which assists in diagnosis.

Even though all of small cell variant cases have been shown to be ALK+ [1], the prognosis is poor. Kinney, et al. discussed a series of 8 patients with small cell variant receiving combination chemotherapy

Table: Reported cases of small cell variant ALCL treated with HSCT.

Patient	Age/Ethnicity/Sex	Presentation	Primary Location	WBC Count (x10 ⁹ /L) / Lymphocytes (%) / Atypical Cells (%)	Therapy	Type of HSCT	Follow-up
1 [9]	4 mo M	NA	BM, LN	NA	MACOP-B; Auto HSCT x 2 after relapse	Auto	Died 10 mo after transplant
2 [9]	12 M	NA	Bone, skin	NA	D-COMP and EBRT; ECP, Auto HSCT after relapse	Auto	CR 26 mo after diagnosis
3 [9]	14 F	NA	LN, skin	NA	D-COMP; Allo HSCT after relapse	Allo	Died 23 mo after transplant
4 [18]	18 Italian F	Few weeks of fever, weight loss, cough, LAD	BM, LN, lung, mediastinum, skin, relapse to CNS, skin	15 / 61% / 90%	CHOP; additional tx after relapse; Allo HSCT from HLA-identical sibling donor while in CR	Allo (HLA-identical)	CR 18 mo after diagnosis
5 [18]	20 mo French F	2 weeks of fever, LAD	BM, liver, LN, spleen, relapse to BM, LN, skin	37.9 peaking to 120 / 72% / 90%	COPAD-M; vinblastine then Allo HSCT from HLA-identical sibling after relapse	Allo (HLA-identical)	Died a few mo after transplant
6 [13]	6 F	Fever, LAD, progressing to respiratory distress	BM, LN, lung, kidneys	60 peaking to 216 / NA / 51%	APO; MIED after poor response; alternating lomustine, vinblastine, and bleomycin and lomustine, vinblastine, and cytarabine after poor response; HLA-identical Allo HSCT with active disease ^a	Allo (HLA-identical)	CR 17 mo after diagnosis
7 [19]	16 M	NA	BM, CNS, liver, LN, lungs, mediastinum, skin, spleen	NA	Unrelated single-mismatch Allo HSCT after PR to initial tx ^b	Allo (single-mismatch)	CR 29 mo after diagnosis
8 [20]	29 African-American M	1 week of fever, HA, myalgias, chills, RUQ pain, anorexia	BM, CNS, liver, LN, pleura, spleen	20 peaking to 81.3 / 17% / NA	Daunorubicin, vincristine, and prednisone; Hyper-CVAD and IT MTX after re-diagnosis; multi-tx regimen after worsening status ^c ; unrelated single-mismatch Allo HSCT after PR ^d	Allo (single-mismatch)	Died 1 mo after transplant from severe GVHD
9 [21]	23 Japanese F	2 weeks of fever, weakness	BM, relapse to lung	24.5 / NA / 5.5%	CHOP; Auto PBSCT while in CR; CHOP after relapse	Auto	CR at time of report
10 [22]	40 Japanese M	Fever, LAD, leukocytosis	BM, liver, LN, pleura, spleen, spread to CNS	34 / NA / 31%	Unknown induction tx; HD-MTX, HD-cytarabine, IT MTX after CNS spread; single-mismatch sibling Allo PBSCT after PR ^e	Allo (single-mismatch)	CR 18 mo after diagnosis
11 (current case)	31 Caucasian American F	3 weeks of fever, HA, LUQ pain, chills, NS, leukocytosis	BM, liver, LN, pleura, spleen, spread to skin	35 peaking to 69.4 / 17% / 14%	Hyper-CVAD A and B and IT MTX; HLA-identical sibling Allo PBSCT after PR ^f	Allo (HLA-identical)	CR 116 mo after diagnosis

^aPrep regimen of TBI, thiopeta, alemtuzumab, etoposide, and cyclophosphamide; ^bPrep regimen of TBI with cranial boost and etoposide; ^cMulti-tx regimen of ifosfamide, carboplatin, and mesna (modified ICE due to elevated liver enzymes) and prednisone, cyclophosphamide, dexamethasone, ifosfamide, methotrexate, cytarabine, doxorubicin, etoposide, vincristine, vindesine, and intrathecal cytarabine (Seidemann regimen/K3 branch of NHL-Berlin-Frankfurt-Münster 90); ^dPrep regimen of TBI and cyclophosphamide; ^ePrep regimen of TBI, etoposide, and cyclophosphamide; ^fPrep regimen of TBI and cyclophosphamide

of who 7 achieved CR. However, 5 relapsed within 2-21 months after remission with a median time to relapse of 10 months [9]. In another case series involving 4 patients, Youd et al. described similar survival data with 2-year OS of 50% and 3-year DFS of 25% [10]. This pattern of initial response to treatment followed by treatment-resistant relapse is in contrast to the common subtype of ALK+ ALCL. Interestingly, the survival data for small cell variant are comparable to those for ALK- ALCL rather than ALK+. In a series of 28 patients of which 4 were diagnosed with ALK- systemic ALCL, Jagasia, et al. demonstrated that 2 achieved CR with initial therapy with 1 relapsing in 212 days. Even after further treatment, OS and EFS were found to be 50% and 0% respectively for patients with ALK- ALCL [11].

ALCL with Leukemic involvement

One potential explanation for the poor prognosis and aggressive nature of small cell variant ALCL is the high incidence of leukemic

involvement. While leukemic peripheral blood involvement is rare in classic ALCL, it is common with the small cell variant. In a case series of 3 patients with leukemic involvement in ALK+ ALCL by Onciu, et al. 2 of the 3 had marrow and nodal evidence of small cell variant. Neither patient achieved a lasting response after chemotherapy, so HSCT was considered. One patient underwent allogeneic transplantation and achieved CR, while the other continued to decline rapidly and died before transplant [13]. As shown by a complete review of cases by Nguyen, et al., poor prognosis is seen throughout all cases of ALCL with leukemic involvement including both the classic type and small cell variant. Of the 21 leukemic cases of ALCL reported, 18 patients had small cell variant ALCL (the other 3 had the classic type), 13 died of their disease with a median survival of 2.75 months, and 3 patients had either relapsed or were still on treatment at the time of report [14].

HSCT in ALCL

There have been a number of reports concerning the efficacy of allo HSCT in ALCL, morphological subtype unspecified. In a retrospective analysis of 27 patients with treatment-refractory ALCL, Le Gouill, et al. reported 5-year OS and EFS of 55% and 48% respectively after allogeneic HSCT [15]. Dodero et al. reported very similar results in a retrospective analysis of 11 patients with ALCL, with 5-year OS and EFS of 54% and 45% respectively post-allogeneic HSCT [16]. In a retrospective analysis of 64 patients with ALCL, He, et al. compared OS and EFS between treatment with conventional chemotherapy and allo PBSCT. Results revealed that 4-year OS and EFS from PBSCT at first remission were not significantly different (90.9% PBSCT vs. 88.3% for chemo, $p = 0.580$ and 81.8% vs. 70.7%, $p = 0.240$ respectively). However, 4-year EFS was significantly better with PBSCT for patients with B symptoms (100% vs. 50.8%, $p = 0.027$) and bulky disease (100% vs. 52.8%, $p = 0.045$) [17]. The efficacy of allogeneic HSCT for refractory or relapsed ALCL suggests a graft-versus-lymphoma effect that may also be beneficial for poor-prognosis morphological subtypes of ALCL such as the small cell variant.

HSCT in small cell variant ALCL

Due to the poor prognosis and lack of continued response to chemotherapy of ALCL, small cell variant, HSCT has been explored as a potential therapy. A total of 11 cases (including this case) of small cell variant ALCL treated with HSCT (3 auto, 8 allo) have been identified in the literature and are presented in Table 1 [9,13,18-22]. Patient age ranged from 4 months to 40 years with a median age of 16 years.. Each of the 11 patients received a different treatment regimen prior to undergoing transplantation and had variable disease statuses at the time of transplant (1 active disease, 4 relapse, 4 PR, 2 CR). Of the 11 patients, 6 were in CR for a median time of 18 months at the time of report publication, with our patient achieving a remarkable 116 months of CR. There do not seem to be significant differences between responses for auto vs. allo HSCT (CR in 2 of 3 auto patients, 5 of 8 allo) or for HLA-identical vs. single-antigen mismatch donors (CR in 4 of 5 HLA-identical patients, 1 of 2 single mismatch), but the sample size is admittedly small. Interestingly, six of these cases are from the last 10 years with 5 of 6 patients having achieved CR after HSCT, potentially indicating that modern advances in the transplantation process have led to an even better response. Due to the promising data including very good recent responses, HSCT appears to be a viable option for treatment of small cell variant ALCL.

Conclusion

In conclusion, we report the case of a 31-year-old female with small cell variant ALCL who has achieved an ongoing CR for 116 months after allogeneic HSCT. A total of eleven cases of HSCT for small cell variant ALCL including this case have been identified in the literature with six of the patients being alive and/or in CR at the time of report. While these results are promising, prospective trials are needed to evaluate the value of HSCT as treatment for small cell variant ALCL.

References

- Stein H, Foss HD, Dürkop H, Marafioti T, Delsol G, Pulford K, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood*. 2000; 96: 3681-3695.
- Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Petersers C, et al. ALK+ lymphoma: clinico-pathological findings and outcome. *Blood*. 1999; 93: 2697-2706.
- Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer*. 2008; 8: 11-23.
- Amin HM, Lai R. Pathobiology of ALK+ anaplastic large-cell lymphoma. *Blood*. 2007; 110: 2259-2267.
- Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008; 111: 5496-5504.
- Arrowsmith ER, Macon WR, Kinney MC, Stein RS, Goodman SA, Morgan DS, et al. Peripheral T-cell lymphomas: clinical features and prognostic factors of 92 cases defined by the revised European American lymphoma classification. *Leuk Lymphoma*. 2003; 44: 241-249.
- Falini B. Anaplastic large cell lymphoma: pathological, molecular and clinical features. *Br J Haematol*. 2001; 114: 741-760.
- Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. *Blood*. 1999; 93: 3913-3921.
- Kinney MC, Collins RD, Greer JP, Whitlock JA, Sioutos N, Kadin ME. A small-cell-predominant variant of primary Ki-1 (CD30)+ T-cell lymphoma. *Am J Surg Pathol*. 1993; 17: 859-868.
- Youd E, Boyde AM, Attanoos RL, Dojcinov SD. Small cell variant of anaplastic large cell lymphoma: a 10-year review of the All Wales Lymphoma Panel database. *Histopathology*. 2009; 55: 355-358.
- Jagasia M, Morgan D, Goodman S, Hamilton K, Kinney M, Shyr Y, et al. Histology impacts the outcome of peripheral T-cell lymphomas after high dose chemotherapy and stem cell transplant. *Leuk Lymphoma*. 2004; 45: 2261-2267.
- Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004; 101: 2788-2801.
- Onciu M, Behm FG, Raimondi SC, Moore S, Harwood EL, Pui CH, et al. ALK-positive anaplastic large cell lymphoma with leukemic peripheral blood involvement is a clinicopathologic entity with an unfavorable prognosis. Report of three cases and review of the literature. *Am J Clin Pathol*. 2003; 120: 617-625.
- Nguyen JT, Condrion MR, Nguyen ND, De J, Medeiros LJ, Padula A. Anaplastic large cell lymphoma in leukemic phase: extraordinarily high white blood cell count. *Pathol Int*. 2009; 59: 345-353.
- Le Gouill S, Milpied N, Buzyn A, De Latour RP, Vernant JP, Mohty M, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Française de Greffe de Moëlle et de Thérapie Cellulaire. *J Clin Oncol*. 2008; 26: 2264-2271.
- Dodero A, Spina F, Narni F, Patriarca F, Cavattoni I, Benedetti F, et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. *Leukemia*. 2012; 26: 520-526.
- He XH, Li B, Zou SM, Dong M, Zhou SY, Yang JL, et al. Efficacy of peripheral blood stem cell transplantation versus conventional chemotherapy on anaplastic large-cell lymphoma: a retrospective study of 64 patients from a single center. *Chin J Cancer*. 2012; 31: 532-540.
- Bayle C, Charpentier A, Duchayne E, Manel AM, Pages MP, Robert A, et al. Leukaemic presentation of small cell variant anaplastic large cell lymphoma: report of four cases. *Br J Haematol*. 1999; 104: 680-688.
- Cesaro S, Pillon M, Visintin G, Putti MC, Gazzola MV, D'Amore E, et al.

- Unrelated bone marrow transplantation for high-risk anaplastic large cell lymphoma in pediatric patients: a single center case series. *Eur J Haematol.* 2005; 75: 22-26.
20. Grewal JS, Smith LB, Winegarden JD 3rd, Krauss JC, Tworek JA, Schnitzer B. Highly aggressive ALK-positive anaplastic large cell lymphoma with a leukemic phase and multi-organ involvement: a report of three cases and a review of the literature. *Ann Hematol.* 2007; 86: 499-508.
21. Sano F, Tasaka T, Nishimura H, Akiyama T, Kubo Y, Matsuhashi Y, et al. Small cell variant of anaplastic large cell lymphoma diagnosed by a novel chromosomal abnormality t(2;5)(3)(p23;q35;p21) of bone marrow cells. *Pathol Int.* 2008; 58: 494-497.
22. Imamura R, Mouri F, Nomura K, Nakamura T, Oku E, Morishige S, et al. Successful treatment of small cell variant anaplastic large cell lymphoma with allogeneic peripheral blood stem cell transplantation, and review of the literature. *Int J Hematol.* 2013; 97: 139-143.