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CASE REPORT

Alectinib maintenance therapy following cord blood transplantation for relapsed pediatric anaplastic large cell lymphoma with central nervous system involvement

Kosuke Tamefusa[1] · Hisashi Ishida[1] · Daisuke Miyahara[1,2] · Takahiro Shiwaku[1] · Motoharu Ochi[1] · Kiichiro Kanamitsu[1,3] · Kaori Fujiwara[1] · Yasuhisa Tatebe[4] · Kana Washio[1] · Tomoyuki Akiyama[2] · Hirokazu Tsukahara[1]

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Abstract
Pediatric ALK-positive anaplastic large cell lymphoma is a rare subtype of non-Hodgkin lymphoma, and approximately 30% of patients relapse following treatment with conventional chemotherapy. Alectinib monotherapy has demonstrated excellent activity in relapsed and refractory ALCL, but its role as a maintenance therapy after hematopoietic cell transplantation is unclear. We experienced a relapse case of pediatric ALK-positive ALCL with central nervous system involvement treated with alectinib maintenance therapy following cord blood transplantation. The patient has maintained complete remission for more than 3 years after transplantation. There were no remarkable adverse effects that led to discontinuation of alectinib.

Keywords Alectinib · Anaplastic large cell lymphoma · Maintenance therapy · Pediatric

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare subtype of non-Hodgkin lymphoma, constituting 10–20% of pediatric lymphomas. Pediatric ALCL is notable for its ALK-positive status in over 90% of cases, and frequently manifests as advanced disease [1, 2]. While short-pulse conventional chemotherapy is commonly used for pediatric ALCL, approximately 30% of patients experience relapse and refractory disease, which poses significant challenges [1–3]. Here, we present a case of pediatric ALK-positive ALCL involving the central nervous system (CNS) that was treated with alectinib maintenance therapy following cord blood transplantation (CBT). The patient has continued alectinib maintenance therapy without severe adverse effects, maintaining complete remission for over 3 years.

Case report

A 10-year-old boy was admitted to our hospital with persistent fever and upper respiratory symptoms. Because he was initially diagnosed with acute disseminated encephalomyelitis, he was treated with glucocorticoids. However, his fever persisted, and enhanced brain magnetic resonance imaging (MRI) revealed an occupied lesion (Fig. 1A). Although we performed a brain biopsy of the mass at diagnosis, the pathological examination only revealed necrotic tissue. Whole enhanced computed tomography showed multiple lymphadenopathy, pleural fluid, and ascites. Biopsies of cervical lymph nodes, pleural fluid, and bone marrow aspirate revealed abnormal cells (Fig. 1B). Immunohistochemical stains were positive for CD30 and ALK (Fig. 1C) and negative for CD3, CD20, BCL2, and PAX5.

✉ Kosuke Tamefusa
tame.ped.1122@gmail.com

1 Department of Pediatrics, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

2 Department of Child Neurology, Okayama University Hospital, Okayama, Japan

3 Department of Pediatrics, National Hospital Organization Okayama Medical Center, Okayama, Japan

4 Department of Pharmacy, Okayama University Hospital, Okayama, Japan

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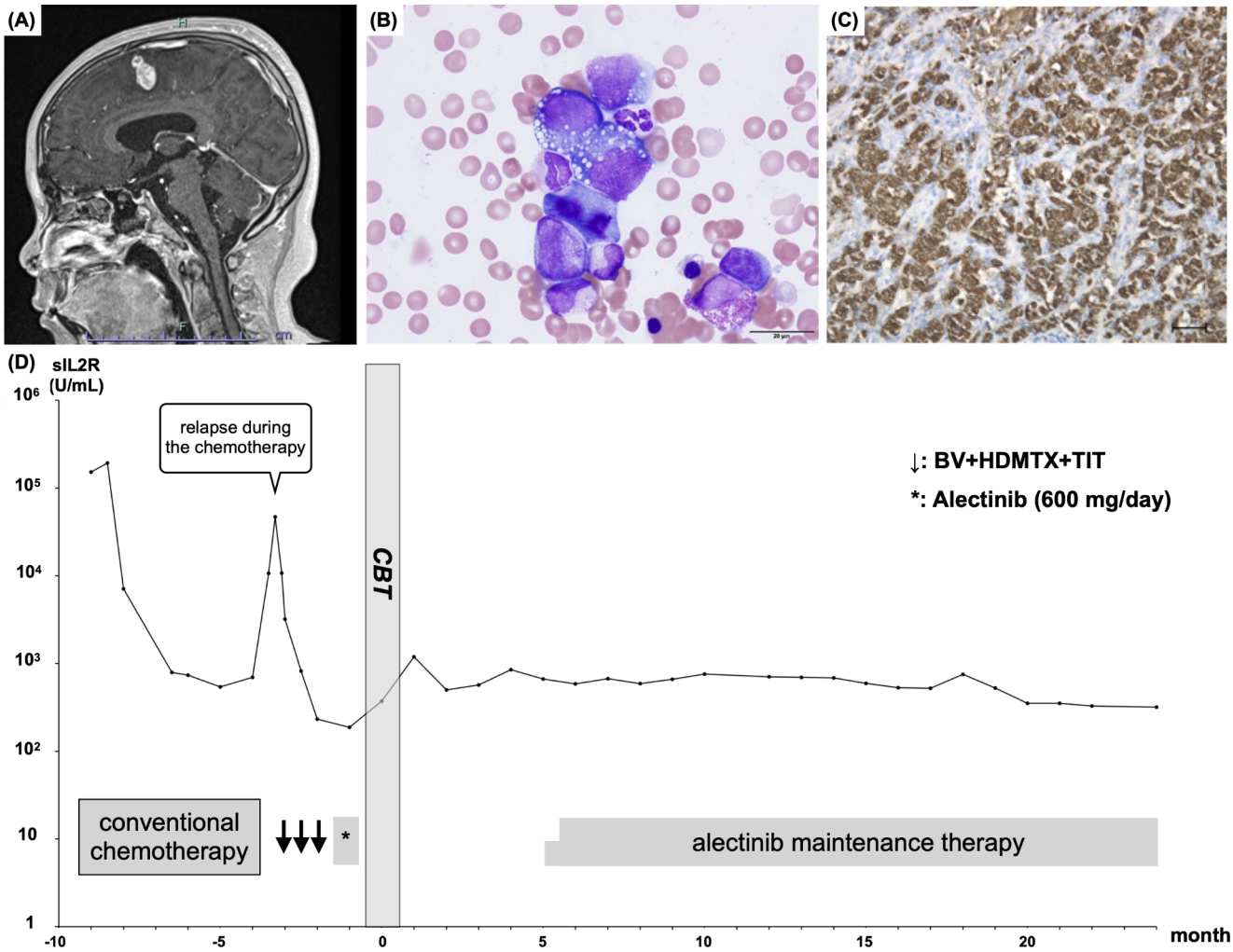

Fig. 1 (**A**) Enhanced magnetic resonance imaging of the brain revealed an occupied lesion. (**B**) Staining of the bone marrow aspirate (May–Giemsa stain) smear at diagnosis. Infiltration of abnormal large cells with high N/C ratio were confirmed. (**C**) Immunohistochemical stains were positive for ALK. (**D**) Illustration of the clinical course of this case from diagnosis. BV, brentuximab vedotin; CBT, cord blood transplantation; HDMTX, high-dose methotrexate; sIL2R, serum soluble interleukin-2 receptor; TIT, triple intrathecal injection

18 F-fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT) revealed systemic uptake (Fig. 2A). Serum soluble interleukin-2 receptor (sIL2R) was elevated to 192,753 U/mL. We could not perform a lumbar puncture at the time of diagnosis owing to his compromised general condition caused by the aggressive progression of lymphoma. However, we considered the brain mass to be lymphoma because of the systemic nature of the disease. The diagnosis was ALK-positive ALCL with stage IV disease according to the St. Jude staging system [4]. Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and dexamethasone was initiated before achieving a pathological diagnosis because of the aggressive nature of his disease. Subsequently, chemotherapy was switched to the JPLSG B-NHL03 protocol [5], avoiding methotrexate for the first two cycles because of pleural effusions and ascites. After five cycles of chemotherapy, PET-CT showed a complete metabolic response (Fig. 2B). However, after six cycles of chemotherapy, hematological recovery was delayed accompanied by sustained fever and bone pain. A bone marrow aspirate revealed lymphoma cells, and sIL2R rebounded to 46,817 U/mL. PET-CT indicated disease relapse (Fig. 2C), and a brain MRI showed that the brain mass remained stable. The result of cerebrospinal fluid cytology was negative. Brentuximab vedotin and high-dose methotrexate chemotherapy, along with intensive intrathecal injections, were initiated following a prior report and remission was successfully achieved [6].

Allogeneic stem cell transplantation (SCT) was planned as the curative treatment owing to relapse during intensive chemotherapy. Alectinib (600 mg/day) was administered as bridging chemotherapy because high-dose methotrexate induced grade 3 hepatic toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events,

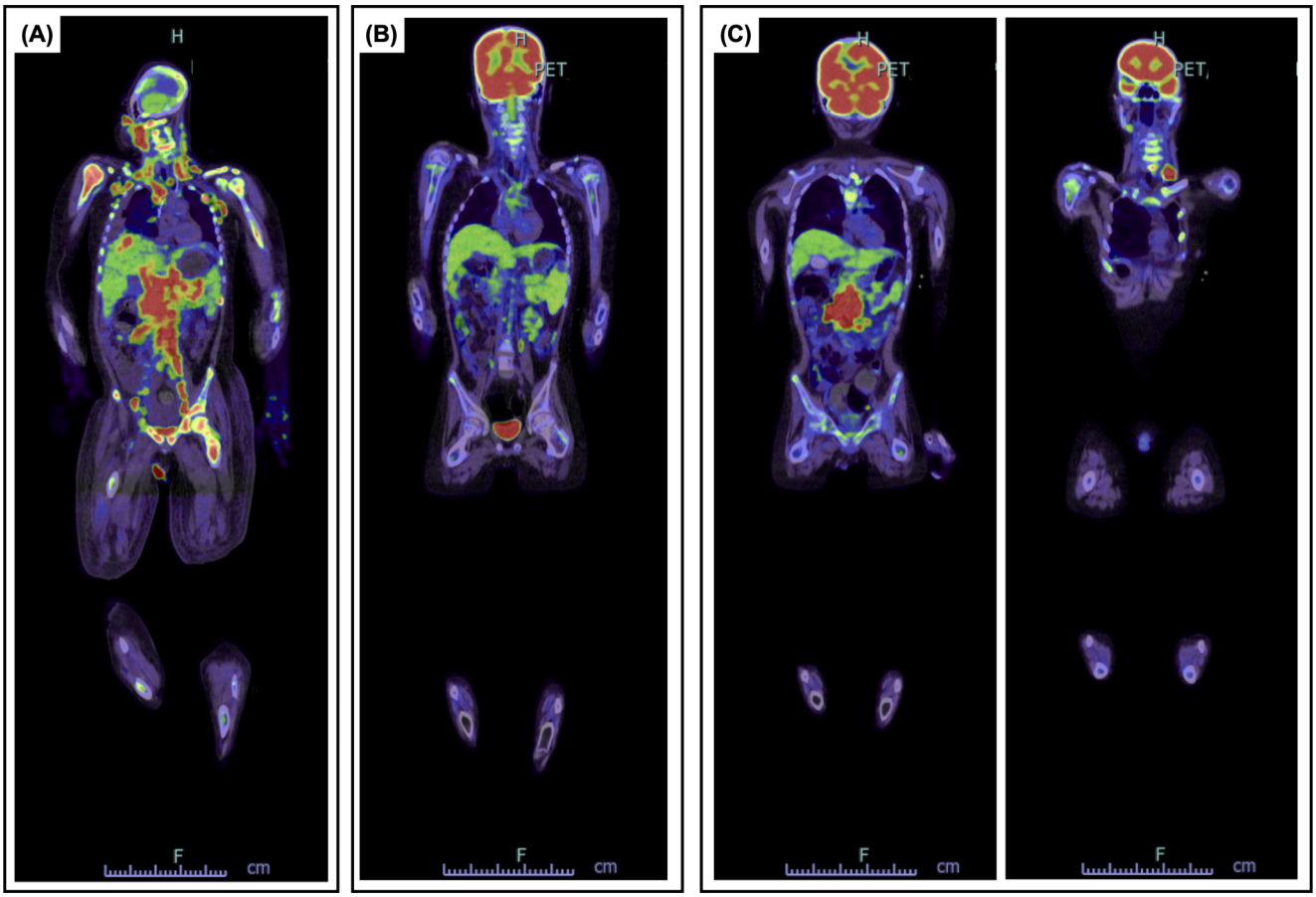

Fig. 2 18 F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) imaging of the patient. (**A**) PET-CT imaging at diagnosis. (**B**) PET-CT imaging after five courses of chemotherapy. (**C**) PET-CT imaging at relapse

version 5.0). The patient proceeded to undergo cord blood transplantation from a human leukocyte antigen two-allele mismatched unrelated donor. The conditioning regimen consisted of fludarabine, melphalan, etoposide, and total body irradiation (4 Gy/2 fr) with graft-versus-host disease (GVHD) prophylaxis including tacrolimus and short-term methotrexate. Grade 1 skin acute GVHD developed, but it resolved with topical steroids. While the patient did not experience severe GVHD and infection soon after CBT, he was pre-emptively treated with rituximab for the Epstein–Barr viraemia overload.

Subsequently, we introduced alectinib as maintenance chemotherapy at post-transplant day 150 because his disease was aggressive and refractory to intensive chemotherapy, and an occupied lesion in the CNS remained on MRI, which was later interpreted as a therapy-related change. We initiated a half-dose (300 mg/day) because his platelet count was slightly decreased to approximately 50,000/μL. We increased the dose of alectinib after confirming the absence of toxicity at post-transplant day 165. He has continued alectinib and remained in remission for more than 3 years after CBT. We have monitored the sIL2R level, and it has remained at almost normal levels. Although he has focal epilepsy, which has been related to prior CNS involvement, no other serious adverse effects have been observed (Fig. 1D).

Discussion

Most treatment protocols have demonstrated approximately 60–70% event-free survival, with early disease relapse being the primary challenge in the current treatment strategy for pediatric ALCL [1–3]. The outcomes for relapsed and refractory ALCL have been unsatisfactory, and a standardized treatment strategy has not been established [1–3, 7]. A study reported 57% 5-year overall survival among 74 children and adolescents with relapsed or refractory ALCL [3]. In this study, 11 of 16 patients receiving allogeneic SCT ($n = 16$) maintained continuous remission. A prospective study, stratifying children with refractory or relapsed ALCL, demonstrated the efficacy of consolidation by allogeneic SCT for cases of high-risk early relapse or refractory

Table 1 Summary of ALK-positive lymphoma cases treated with post-transplant ALK inhibitors

#	Age	Sex	CNS disease	Therapies before SCT	SCT	Conditioning	ALK inhibitor	Initiation timing	AEs of ALK inhibitor	Disease status	Treatment duration	Reference
1	34	M	Positive	CHOP, Gem-based regimen, BV, crizotinib etc.	PBSCT	MAC	Crizotinib	Day 21	Transient thrombocytopenia	Remission	30 months	Cleary JM, et al. *J Natl Compr Canc Netw*. 2014
2	38	NA	NA	CHOP, DHAP, VIM	BMT	NA	Crizotinib	Day 90*	Abnormal liver function	Remission	8 months	Gambacorti Passerini C, et al. *J Natl Cancer Inst*. 2014
3	27	M	Positive	CHOPE + HDMTX, alectinib	Allo-SCT	NA	Alectinib	Day30**	Papular rash	Remission	NA	Reed DR, et al. *Clin Lymphoma Myeloma Leuk*. 2019
4	18	F	Positive	ALCL99	CBT	FLU + BU + MEL	Alectinib	Day 40	NA	Remission	Over 16 months	Saito S, et al. *Medicine (Baltimore)*. 2021
5	20	F	Negative	CHOPE	Haplo-PBSCT	NA	Crizotinib	1 month after PBSCT	Gastrointestinal symptoms	Remission	3 months	Sun X, et al. *Indian J Cancer*. 2021
6	10	M	Positive	CHODEX, B-NHL-03, BV + HD-MTX	CBT	VP16 + FLU + MEL + TBI	Alectinib	Day 150	Transient thrombocytopenia	Remission	Over 3 years	Current case

AEs, adverse effects; Allo, allogeneic; BMT, bone marrow transplantation; BU, busulfan; BV, brentuximab vedotin; CBT, cord blood transplantation; CHODEX, cyclophosphamide + doxorubicin + vincristine + dexamethasone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CHOPE, CHOP + etoposide; CNS, central nervous system; DHAP, dexamethasone + cytarabine + cisplatin; F, female; FLU, fludarabine; Gem, gemcitabine; M, male; MAC, myeloablative conditioning; MEL, melphalan; NA, not available; PBSCT, peripheral blood stem cell transplantation; SCT, stem cell transplantation; TBI, total body irradiation; VIM, etoposide + ifosfamide + mitoxantrone; VP16, etoposide

*Relapse was confirmed at day 90 after allo-BMT, **extranodal disease was proven by biopsy on day 30 and alectinib was restarted

disease [7]. However autologous SCT did not prevent additional relapses.

In ALK-positive ALCL, the activated *ALK* mutation acts as a driver mutation, making the blockade of ALK an ideal therapeutic target [1, 2, 8]. While some clinical trials have demonstrated the efficacy of crizotinib, data on alectinib for pediatric ALCL are limited. Alectinib is reported to have higher efficacy and safety for ALK-positive tumors compared with crizotinib because alectinib is more specific [1, 8, 9]. Alectinib is also known for its effective penetration into the CNS [8]. In a phase II clinical trial conducted in Japan, alectinib exhibited favorable clinical activity and was well-tolerated in children with ALK-positive ALCL [9]. Despite the small sample size, 8 out of 10 patients achieved objective responses (6 with complete remission and 2 with partial remission).

Because of the poor prognosis associated with early relapsed ALCL, even when treated with allogeneic SCT [3, 7], and considering the highly aggressive clinical symptoms presented in our case, we initiated alectinib maintenance therapy after CBT. This case had CNS involvement and we deemed alectinib to be preferable as an ALK inhibitor over crizotinib. While some lymphoma cases treated with post-SCT ALK inhibitors have been reported, data on pediatric ALCL remain limited (Table 1). Our patient continued alectinib without severe adverse effects and maintained complete remission for over 3 years. The use of maintenance therapy after SCT is not well-established, and the duration of such therapy is still under discussion. Further data on the use of alectinib for pediatric ALCL, especially in the SCT setting, are imperative.

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Author contributions K.T. wrote the manuscript. K.T., H.I., D.M., T.S., M.O., K.K., K.F., Y.T., K.W., and T.A. provided medical care for the patients. K.W. and H.T. revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability The data described in this case report are available from the corresponding author upon reasonable request.

Declarations

Ethical approval Written informed consent was obtained from the patient and his guardian for the publication of this case report.

Competing interests The authors declare no competing interests.

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