



## Hematological Malignancies

## Role of ALK Inhibitors in Anaplastic Large Cell Lymphoma—Experience from an Indian Center

Muthiah Vaikundaraja Indhuja<sup>1</sup> Sivasree Kesana<sup>1</sup><sup>1</sup> Nikita Mehra<sup>1</sup> Parathan Karunakaran<sup>1</sup><sup>1</sup>  
 Arun Kumar Rajan<sup>1</sup> Venkatraman Radhakrishnan<sup>1</sup><sup>1</sup> Perumal Kalaiyarasi Jayachandran<sup>1</sup><sup>1</sup>

<sup>1</sup>Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

**Address for correspondence** Perumal Kalaiyarasi Jayachandran, MD, MRCP (UK), D.M., F.R.C.P. (Glasg), Department of Medical Oncology, Cancer Institute (WIA), 38, Sardar Patel Road, Guindy, Chennai, Tamil Nadu, India-600036 (e-mail: dr.pkjayachandran@gmail.com).

South Asian J Cancer 2024;13(2):121–125.

## Abstract



Perumal Kalaiyarasi Jayachandran

## Keywords

- ▶ ALK+ ALCL
- ▶ anaplastic large cell lymphoma
- ▶ crizotinib in ALCL
- ▶ ALK inhibitors in ALCL
- ▶ relapsed refractory ALCL
- ▶ targeted therapy in NHL

Anaplastic large cell lymphoma (ALCL) is the second most common type of peripheral T cell lymphoma and an aggressive mature T cell lymphoma. About 50 to 70% of systemic ALCLs are anaplastic lymphoma kinase positive (ALK +), the proportion even higher in the pediatric population. The 5-year survival after chemotherapy is around 70 to 80%. But there is a subgroup of ALK+ ALCL patients who are refractory to chemotherapy. Brentuximab vedotin is an approved agent for such patients. The activity of ALK inhibitors in ALK+ non-small cell lung cancer is well known and has been approved for use. The efficacy and safety of ALK inhibitors in ALK + ALCL are largely under-reported. Here we have reported our experience in the use of ALK inhibitors in relapsed refractory ALK+ ALCL.

## Introduction

Chromosomal rearrangements resulting in oncogenic fusions and activation of the tyrosine kinase domain of anaplastic lymphoma kinase (ALK) drive the tumorigenesis in many cancers. About 50 to 70% of patients with anaplastic large cell lymphoma (ALCL) have ALK fusions. ALK-positive ALCL (ALK+ ALCL) is unique in the way that it has its origin in the thymus like T lymphoblastic lymphoma but has a peripheral distribution like peripheral T lymphoblastic lymphoma.<sup>1</sup>

A specific translocation t(2;5) (p23,q35) involving the fusion of the gene of the nucleolar shuttling protein nucleophosmin (*NPM1*) to the gene of the receptor tyrosine kinase *ALK* is detected in more than 85% of ALK +ALCL cases.<sup>2</sup> ALK+ ALCL has a 5-year overall survival of 70 to 80% and is generally chemo-sensitive. However, relapses do occur and they portend a bad prognosis. All conventional salvage chemotherapies have shown poor outcomes. Only brentuximab vedotin (anti-CD30 monoclonal antibody toxin conjugate) had shown a complete response (CR) rate of 57% and a

DOI <https://doi.org/10.1055/s-0042-1758353> ISSN 2278-330X

**How to cite this article:** Indhuja MV, Kesana S, Mehra N, et al. Role of ALK Inhibitors in Anaplastic Large Cell Lymphoma—Experience from an Indian Center South Asian J Cancer 2024; 13 (2):121–135.

© 2023. MedIntel Services Pvt Ltd. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

median progression-free survival of 14.6 months.<sup>3</sup> Crizotinib has been approved for use in relapsed refractory ALK+ ALCL by the U.S. Food and Drug Administration in pediatric patients of 1 year of age and older and young adults based on a multicenter single-arm open-label phase I/II study.<sup>4</sup> Other ALK inhibitors have not been approved in ALCL. In this case series, we have reported our experience of ALK inhibitors—crizotinib and ceritinib in relapsed refractory ALK+ ALCL.

## Methods

This is retrospective case series. We have included ALCL patients who have received ALK inhibitors as treatment. The cases were identified by keyword search in our hospital software in lymphoma patients with the prescription of ALK inhibitors. After identification of the patients, the data collection was done from the case records regarding the stage at presentation, previous lines treatment, response, toxicity, and survival. The follow-up of these patients was made as per institutional protocol. Clinical examination was done once in 3 months for 3 years and once in 6 months subsequently. After demonstration of CR, imaging was done if there was a suspicion of relapse. In addition to these complete blood counts, liver function tests were done monthly for the initial 3 months and thereafter if clinically indicated.

Off-label consent has been taken from all patients as ALK inhibitors have not been approved for use in ALCL in our country. Crizotinib was used at a dose of 250 mg per os (PO) twice daily (pediatric patients were given at the dose of 280 mg/m<sup>2</sup>). Ceritinib was used at a dose of 450mg PO once daily in adults and 150mg PO once daily in one pediatric patient. As per our institutional policy, retrospective case series do not require an ethical committee approval.

## Results

We have identified about five patients between 2015 an 2019 and one patient in 2022 who have been prescribed ALK inhibitors for ALK+ ALCL. The median age at diagnosis was 27.5 years (range: 10–44). Four patients were adult and two were pediatric. There were two patients each with Stage II, III and IV disease.

Five out of six patients were chemo-refractory to their previous line of treatment. ALK inhibitors were used in fourth line in two patients, third line in three patients, and second line in one patient. One adult patient had bone marrow involvement with hemophagocytic lymphohistiocytosis and was in a poor performance status. He was given crizotinib in the second line due to poor chemo-tolerance and progression on the low-intensity chemotherapy.

All the six patients who were chemo-refractory achieved CR within 2 to 3 months of starting ALK inhibitors and continued to be in CR till the last follow-up. One had a consolidation allogeneic matched sibling transplant after

3 months of ALK inhibitor and he was not continued on ALK inhibitor posttransplant. One other patient could not continue the ALK inhibitors due to financial reasons after 2 years and hence the patient was taken up for consolidation allogeneic haploidentical stem cell transplantation but unfortunately the patient expired due to transplant-related mortality. The median follow-up of the study series was 3.79 years (range: 0.25–8.08 years). Five patients were disease free and alive at the time of study.

Toxicities were recorded. Out of six patients, two patients had pedal edema. Two patients had grade ½ diarrhea. There was no dose-limiting toxicity. The detailed characteristics of all the patients have been described in [Table 1](#).

## Discussion

ALCL is a unique subset of T cell lymphomas, occurring predominantly in the younger population and constitutes approximately 15% of non-Hodgkin's lymphoma in children. It is more common in males than in females. According to the 2016 WHO classification, ALCL can be classified into ALK+ ALCL, ALK negative (ALK –) ALCL, primary cutaneous ALCL, and breast implant-associated ALCL. About 50 to 70% of ALCL are ALK+.

ALK+ ALCL generally has good prognosis than their ALK– counterparts. The 5-year overall survival is around 70 to 80%. Anthracycline-containing regimens like CHOPE are the treatment regimen commonly used in adults and in the pediatric population short pulse, high intensity chemotherapy like LMB protocol is used. Since the overall prognosis of ALK+ ALCL is good, unlike other T cell lymphomas, consolidation with autologous stem cell transplantation is not recommended after first remission. Frontline treatment of brentuximab vedotin with CHP has also been approved with an improvement in overall survival. Relapses occur frequently in around 30 to 40% of patients, which portends a bad prognosis.<sup>5</sup> ALK inhibitors have been tried in a relapsed refractory setting, especially in the pediatric population.<sup>6,7</sup> Crizotinib is an orally available small-molecule tyrosine kinase inhibitor that inhibits ALK, cMET (mesenchymal-epithelial transition factor), and ROS1 (receptor tyrosine kinase). Ceritinib is a selective and more potent ALK inhibitor.

Our study is unique in a way that it has shown 100% CR rates in the population that is refractory to two lines of treatment. It has also shown a durable complete remission in all the patients.

There are only a few case series demonstrating the activity of crizotinib in ALK+ ALCL. In a case series of 11 patients with advanced chemoresistant ALK+ ALCL/DLBCL, crizotinib usage has been associated with an overall response rate (ORR) of 90.2%; responses were seen in 10 out of 11 patients within 1 month of starting treatment. Four patients were in complete remission with crizotinib administration, four had disease progression, one patient underwent an allogeneic transplant after attaining CR with crizotinib, and two other patients had used crizotinib before and/or after allogeneic transplant and are currently not on crizotinib usage. The common side effects noted were ocular flashes, skin rash, and

**Table 1** Characteristics of patients on ALK inhibitors

No	Age/ Sex	Stage	1st line	2nd line	3rd Line	4th Line	Best response to ALK inhibitor	Time to achieve best response	Comments
1	37/F	III	CEOP x 5—due to cardiac dysfunction PET—progression	GDP x 1 Clinical progression	Weekly vinblastine X 2 Clinical progression	Ceritinib 450 mg OD Oct 2019	Clinical CR PET-CT was done after 6 months—also CR	2 months	Was on ceritinib for 2 years and was taken up for consolidation haplo-identical transplant—died due to complications of transplant
2	23/M	IV	CHOP-E x 6 PET—refractory disease/ minimal progression	GDP x 1 Clinical progression	Weekly vinblastine X 2 Clinical progression	Crizotinib 250 mg BD Dec 2017	PET—CR	2 months	Was continued on crizotinib for 4 months and then underwent allogeneic SCT. Posttransplant Crizotinib was stopped and patient is alive with no disease
3	10/F	III	LMB 89 PET—CR DFS—3.3 years	Weekly vinblastine X 2 No response	Crizotinib 250mg OD— 5 days a week Jan 2018		PET—CR	3 months	On crizotinib for the past 4 years in CR
4	10/M	II	LMB 89 PET—CR DFS—3 months	Weekly vinblastine X 2 No response	ICE chemotherapy with Ceritinib 150 mg OD May 2019		PET—CR	3 months	ICE was given 3 cycles and then continued only on ceritinib for the past 3 years in CR
5	44/F	II	CHOP x 1 Clinical progression	LMB 89 PR	Crizotinib 250 mg BD June 2014		PET—CR	6 months	On Crizotinib for the past 7.5 years in CR
6	32/M	IV	50% CHOP x 1; 50%CHOP-E x 2 Could not tolerate intensive chemotherapy due to associated HLH	Crizotinib 250mg BD April 2022			Clinical CR	3 months	After 1 <sup>st</sup> cycle of CHOP, he was put on crizotinib for 1 month. The counts normalized and he was restarted on CHOP chemotherapy. But after 3 cycles, he had clinical progression in the form of new nodes and pancytopenia and hence he was restarted on crizotinib

Abbreviations: ALK, anaplastic lymphoma kinase; BD, twice daily; CEOP, cyclophosphamide, etoposide, vincristine, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CHOPE, cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide; GDP, gemcitabine, dexamethasone, cisplatin; HLH, hemophagocytic lymphohistiocytosis; LMP, lymphoma malignant B cell; OD, once daily; PET-CR, positron emission tomography—complete response.

**Table 2** Comparison of our case series with other studies using ALK inhibitors in ALK+ ALCL

	Our case series	Case series by Gambacorti Passerini C et al <sup>8</sup>	Phase 2 prospective study by Mossé et al —ALK + ALCL cohort <sup>7</sup>		Phase 1 dose finding study by Mossé et al—ALK + ALCL cohort <sup>6</sup>
Number	6	11 (ALK + ALCL—9; ALK + DLBCL—2)	26		9
Drug used	Crizotinib—4; Ceritinib—2	Crizotinib	Crizotinib 165 mg/m <sup>2</sup> (n = 6)	Crizotinib 280mg/m <sup>2</sup> (n = 20)	Crizotinib (at various dose levels)
Overall response rate	100%	90.2%	83%	90%	88.8%
Complete response rate	100%	63.6%	80%	80%	77.7%
Toxicities	Peripheral edema—33% Diarrhea—33%	Peripheral edema—27.7% Neutropenia—18% Ocular flashes—90% Rash—9%	<sup>a</sup> Peripheral edema—0%	0%	Toxicities not reported separately
			<sup>a</sup> Neutropenia—33%	70%	
			<sup>a</sup> Diarrhea—0%	3.8%	

Abbreviations: ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; DLBCL, diffuse large B cell lymphoma.

<sup>a</sup>Only grade 3/4 toxicities were reported.

peripheral edema. Laboratory abnormalities included neutropenia, thrombocytosis, and liver function test elevation.<sup>8</sup> The response rates were 100% in our study series as compared with other studies may be explained by the small number of population in our series. In another case series by Mossé et al of 40 pediatric patients with ALK+ tumors (26 with relapsed refractory ALK+ ALCL and 14 patients with metastatic or inoperable inflammatory myofibroblastic tumor, the ORR for patients with ALK+ALCL treated with Crizotinib doses at 165mg/m<sup>2</sup> and 280mg/m<sup>2</sup> were 83% and 90% respectively, CR rates were around 80% in both doses. The most common grade 3/4 adverse event was neutropenia.<sup>7</sup> But in our series, we did not find any neutropenia both in adult and pediatric populations. The comparison of the above studies has been showed in **Table 2**.

The main mechanism of resistance to crizotinib in ALCL is the overexpression of ALK-NPM1 fusion kinase, unlike in non-small cell lung cancer, where resistance is mainly due to activation of alternate pathways or second-site kinase-domain mutations. This resistance pattern also leads to toxic signaling overdose upon withdrawal of TKI. This is the reason why most patients develop abrupt disease symptoms upon withdrawal of ALK inhibitors in ALCL. Interferon-gamma (through its inhibition of STAT 3 by activating STAT 1), along with ALK inhibitors, can be tried in such cases to overcome the resistance to ALK inhibitors.<sup>9</sup>

ALK inhibitors induce long-term remission in patients with relapsed refractory ALK+ ALCL, but these drugs have to be continued till progression. Most ALK inhibitors are very costly and patients do not afford them for a longer duration. Consolidation with allogeneic stem cell transplantation after achieving complete remission with ALK inhibitors is a

strategy to reduce the cost burden of the long-term use of the drugs. Nevertheless, the toxicities of allogeneic stem cell transplantation would obscure the benefit of cost-effectiveness like one patient in our series who died due to transplant-related mortality.

## Conclusion

This is the first case series about the usage of ALK inhibitors in ALK + ALCL from India. In relapsed refractory ALCL post multiple lines of therapy ALK inhibitors have shown to induce complete response in both adult and pediatric patients within 6 months of starting treatment. The adverse events were very minimal and ALK inhibitors very well tolerated.

## Funding

There were no external sources of funding for this project.

## Conflict of Interest

None declared.

## References

- 1 Turner SD. An exploration into the origins and pathogenesis of anaplastic large cell lymphoma, anaplastic lymphoma kinase (ALK)-positive. *Cancers* (Basel) 2017;9(10):141
- 2 Falini B, Martelli MP. Anaplastic large cell lymphoma: changes in the World Health Organization classification and perspectives for targeted therapy. *Haematologica* 2009;94(07):897–900
- 3 Horwitz S, O'Connor OA, Pro B, et al; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* 2019;393(10168): 229–240

- 4 Foster JH, Voss SD, Hall DC, et al. Activity of crizotinib in patients with ALK-aberrant relapsed/refractory neuroblastoma: a children's oncology group study (ADVL0912). *Clin Cancer Res* 2021;27(13):3543–3548
- 5 Zhang XR, Chien PN, Nam SY, Heo CY. Anaplastic large cell lymphoma: molecular pathogenesis and treatment. *Cancers (Basel)* 2022;14(07):1650. Doi: 10.3390/cancers14071650
- 6 Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol* 2013;14(06):472–480
- 7 Mossé YP, Voss SD, Lim MS, et al. Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a children's oncology group study. *J Clin Oncol* 2017;35(28):3215–3221
- 8 Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst* 2014;106(02):djt378. Doi: 10.1093/jnci/djt378
- 9 Sundara Rajan S, Dipak Amin A, Li L, et al. NPM1-ALK overexpression-driven toxicity in ALCL is partner dependent and mediated by STAT1 antagonism of STAT3 survival signaling, revealing a novel therapeutic strategy. *Blood* 2017;130(Suppl 1):2506. Doi: 10.1182/blood.V130.Suppl\_1.2506.2506