Profound and sustained response with next-generation ALK inhibitors in patients with relapsed or progressive ALK-positive anaplastic large cell lymphoma with central nervous system involvement

Anaplastic large cell lymphoma (ALCL) is a rare disease accounting for less than 15% of all non-Hodgkin lymphomas in childhood. In children and adolescents, more than 90% of cases of ALCL harbor a translocation involving the anaplastic lymphoma kinase (ALK) gene, leading to constitutive activation of the ALK-kinase.[1] Outcome is good in most patients with a 5-year overall survival reaching 90% according to recent reports.[2] Involvement of the central nervous system (CNS) at diagnosis or at relapse/progression is uncommon with a 5-year cumulative risk of 4%.[3]

ALK inhibitors have now been used for several years in patients with relapsed ALK-positive ALCL with response rates ranging from 53% to 90%.[4–6] Most previous trials were based on the first-generation ALK inhibitor, crizotinib, which is known to have poor CNS penetration. By contrast, next-generation ALK inhibitors, which have been developed for lung cancer and brain metastases, have good CNS penetration and could therefore be of great interest for treating patients with ALK-positive ALCL and CNS involvement. We prospectively collected data on all French patients <22 years old treated between 2017 and 2020 with next-generation ALK inhibitors for a CNS relapse/progression of ALK-positive ALCL.

Ten patients, suffering from 11 CNS relapses/progression, were identified. Data for each individual and details of each CNS relapse/progression are available in Tables 1 and 2 and *Online Supplementary Table S1*.

One patient only had CNS involvement at diagnosis. Of note, all patients underwent a diagnostic cerebrospinal fluid evaluation as routine staging. CNS imaging was only performed in cases of clinical suspicion. Three patients had a leukemic presentation or bone marrow involvement at diagnosis and six had no particular clinical risk factor for CNS evolution (Table 1). Of note, at frontline therapy, all patients at diagnosis, except for one, were at high risk of relapse or progression with minimal disseminated disease and minimal residual disease after one course of treatment. Five patients experienced disease progression while on frontline therapy. For the five others who achieved complete remission and completed the frontline therapy schedule, the time from end of treatment to the first relapse ranged from 0.6 to 2.1 months.

CNS disease was diagnosed during frontline treatment in one patient, at the first relapse in five and after the second or further relapse in four. The median age at CNS relapse/progression was 11 years (range, 1.8-19). The median delay between diagnosis and CNS relapse/progression in the nine patients free of CNS involvement at diagnosis was 9 months (range, 1.6-54). Before the initiation of treatment with next-generation ALK inhibitors, all patients had received one to three previous treatment lines and four of them had received crizotinib (*Online Supplementary Table S1*). Interestingly, nine patients had positive minimal residual disease while on the treatment line preceding CNS relapse/progression although eight were in complete clinical and radiological remission. Of note, six patients had CNS relapse while on treatment, with either vinblastine (n=3) or crizotinib (n=3). At the time of CNS progression/relapse, four patients had only CNS involvement and the six others also had systemic disease. CNS involvement was restricted to the presence of tumor cells on cytological examination in the cerebrospinal fluid in three patients, while seven had intracranial masses, associated with cerebrospinal fluid positivity on cytological examination in three of the five in whom the cerebrospinal fluid could be examined.

Among the 11 episodes of CNS relapse/progression reported here, the next-generation ALK inhibitor used was ceritinib (n=3), lorlatinib (n=3) or alectinib (n=5). The median duration of the treatment with a next-generation ALK inhibitor was 11.3 months (range, 1.2- 27.2). Regarding response to these ALK inhibitors, we report ten responses in the 11 episodes of CNS relapse/progression. One progression of disease occurred on ceritinib in patient #5 who finally achieved complete remission after being switched to high-dose methotrexate followed by alectinib. The median time to best response was 1.5 months (range, 0.5-6) (Figure 1). Only one patient experienced systemic and CNS disease relapse after achieving complete remission on alectinib (patient #9). This progression was not well documented either on a molecular level (i.e., resistance mutation) or on a pharmacokinetic level. Alectinib was stopped and this patient benefited from CNS-directed chemotherapy and finally achieved third complete remission. She unfortunately died while in this third complete remission in the context of an invasive mucormycosis infection.

Regarding the nine patients with prolonged complete re-

Table 1. Patients' initial diagnosis and relapse characteristics.

	Disease characteristics at diagnosis					Characteristics of CNS relapse treated with a next-generation ALK inhibitors					
Patient (age at diagnosis in years)	**Initial CNS status**	**Other clinical risk factors for CNS at diagnosis***	**MDD/ early MRD status in frontline**	**Histological pattern (SC/LH component *vs.* common)**	**Time from EOT to first relapse (months)**	**Interval between initial diagnosis and CNS involvement (months)**	**Number of relapse/ progression (type)**	**Last treatment before CNS relapse**	**Peripheral blood MRD status on previous treatment line**	**Type of relapse**	**Type of CNS involvement**
1 (16)	negative	no	positive/ positive	common	0.7	54	3, relapse	vinblastine	positive	systemic and CNS	CNS mass (CSF nd)
2 (6)	negative	leukemic presentation (blood circulating cells on cytologoly)	positive/ positive	SC/LH	on therapy	4.9	3, progression	vinblastine	positive	systemic (including uncontrolled leukemic form) and CNS	multiple CNS masses + CSF positive
3 (19)	positive	na	nd	common	on therapy	na	1, progression	radio-therapy	positive	systemic and CNS	CNS mass (CSF nd)
4 (11)	negative	biopsy of choroid plexus papilloma at treatment initiation.	positive/ positive	common	on therapy	4.1	1, relapse (on biopsy route while on vinblastine for recovery post CNS biopsy)	vinblastine	positive	CNS only	multiple CNS masses
5 (9)	negative	no	positive/ positive	SC/LH	2.1	10.1	1, relapse	ALCL99	negative at EOT with ALCL99	systemic and CNS	CSF positive only
6 (1.8)	negative	BM involvement (diagnosed on cytology)	positive/ positive	SC/LH	on therapy	1.6	1, relapse	ALCL99	positive	systemic (including BM) and CNS	CSF positive only
7 (11)	negative	no	positive/ positive	nd	on therapy	9	2, relapse	crizotinib	positive	CNS only	CNS mass + CSF positive
8 (13)	negative	no	positive/ positive	nd	1.5	5.8	1, relapse	ALCL99	positive at EOT with ALCL99	systemic and CNS	CSF positive only
9 (4)	negative	BM involvement (diagnosed on cytology), severe HLH	positive/ positive	SC/LH	1.9	15.8	2, relapse	crizotinib	positive	CNS only	CNS mass
10 (19)	negative	no	positive/ positive	SC/LH	0.6	14.8	2, relapse	crizotinib	positive	CNS only	multiple CNS masses + CSF positive

*Leukemic presentation, bone marrow involvement, central nervous system involvement at diagnosis. CNS: central nervous system; MDD: minimal disseminated disease; early MRD: early measurement (after one chemotherapy course) of minimal residual disease; SC: small cell component; LH: lymphohistiocytic component; EOT: end of treatment; CSF: cerebrospinal fluid; nd: not done; na: not applicable; BM: bone marrow; HLH: hemophagocytic lymphohistiocytosis.

mission, four patients were still on ALK inhibitors at the date of the last follow-up visit. The treatment had been discontinued in the other five patients for various reasons: one patient (#8) underwent allogeneic hematopoietic stem cell transplantation after complete remission; one patient (#3) stopped ceritinib because of grade 3 toxicity and was switched to weekly vinblastine for 3 months and received no further treatment after vinblastine, with a fol-

low-up time off lymphoma therapy of 42 months; two patients (#1 and #6) were included in the NIVOALCL trial (NCT03703050) and received nivolumab while still in complete remission; and one patient (#5) definitively stopped the next-generation ALK inhibitor and received no further therapy, with more than 10 months off treatment at the date of last follow-up considered for the study.

Overall, nine out of ten patients were alive in complete remission at the date of last visit. The median duration of the follow-up from the initiation of ALK inhibitor treatment in these nine patients was 24.2 months (range, 11.3-48.1).

Of note, next-generation ALK inhibitors could be helpful in critically ill patients as clinical improvements occurred very fast; for example, patient #3 was in a coma at treatment initiation and regained normal consciousness. Response on imaging was also impressive for the patients with intracranial masses (*Online Supplementary Figure S1*).

Regarding tolerance of next-generation ALK inhibitors, we reported notable adverse events of grade 3 or higher in eight patients, including weight gain in three patients, neuropsychological manifestations in three patients and

Table 2. Response to next-generation ALK inhibitors and patients' outcome.

Patient	Name of ALKi	Type of CNS involvement	Best response	Time to best response (months)	Treatment duration (months)	Next treatment after ALKi	Notable adverse events	Current outcome and disease status (FU from ALKi initiation, in months)
1	lorlatinib	CNS mass (CSF nd)	CR	6	7	other investigational treatment in CR for consolidation	hallucinations, anxiety grade 3	alive in CR (30.2)
2	alectinib	multiple CNS masses + CSF positive	CR	1.6	14.5	na	weight gain grade 3	alive in CR (14.5)
3	ceritinib	CNS mass (CSF n.d.)	CR	0.5	3	vinblastine 3 months then no further treament	GI toxicity grade 3	alive in CR (48.1)
4	lorlatinib	multiples CNS masses	CR	1	27.2	na	weight gain grade 3	alive in CR (27.2)
5	ceritinib	CSF positive	PD	1.2	1.2	na	hepatic toxicity grade 3	alive in CR
5 (2nd episode treated with ALKi)	alectinib	CSF positive	CR	n.a.(CR obtained with 2 courses of HD MTX)	26	no further treatment	weight gain grade 3	alive in CR (36.5)
6	ceritinib	CSF positive	CR	1.3	16.9	other investigational treatment in CR for consolidation	GI and hepatic toxicity grade 3	alive in CR (40.8)
7	lorlatinib	CNS mass + CSF positive	CR	1.6	21	na	irritability and aggression grade 2	alive in CR (21.0)
8	alectinib	CSF positive	CR	2.5	2.9	allogeneic transplant in CR	none	alive in CR (19.1)
9	alectinib	CNS mass	CR	1.4	2.5	CNS-directed chemo-therapy for CNS disease progression	none	died, in CR3 in context of mucor-mycosis infection (9.4)
10	alectinib	multiple CNS masses + CSF positive	CR	3.6	11.3	na	acute delirium Grade 3	alive in CR (11.3)

ALKi: ALK inhibitors; CNS: central nervous system; FU: follow-up; CSF: cerebrospinal fluid; nd: not done; CR: complete response; na: not applicable; GI: gastrointestinal; PD: progressive disease; HD-MTX: high-dose methotrexate; CR3: third complete response.

grade 3 gastrointestinal and/or hepatic adverse events in three patients.

In contrast to the overall population of patients with ALK-positive ALCL, patients with CNS involvement any time during the course of their disease are known to have a dismal outcome.[7,8] This was recently confirmed in a report from the European Inter-Group for Childhood Non-Hodgkin Lymphoma, in which the 3-year overall survival of patients after CNS relapse was less than 50%, and the median time to death after CNS relapse was 3.5 months in the 4% of patients experiencing such relapses.[3]

The range of therapeutic options for relapsed/refractory ALK-positive ALCL has increased significantly during the past decades. Besides conventional chemotherapy, several targeted therapies such as brentuximab vedotin and ALK inhibitors are now widely used to treat patients with ALCL at relapse.[4,9] However, there is no evidence that vinblastine and the antibody-drug conjugate brentuximab vedotin cross the blood-brain barrier,[10] and several cases of CNS relapses occurring in ALCL patients treated with vinblastine or brentuximab for systemic disease have been reported.[11,12]

ALK inhibitors have been used for several years now, with some success. The first-in-class, crizotinib, showed quite good results in relapsed/refractory ALK-positive ALCL.[4–6] However, it might not be efficient for CNS prophylaxis. Indeed, CNS progression during crizotinib treatment is one of the common modes of failure in patients treated for ALK-rearranged non-small cell lung cancer, accounting for nearly 70% of the treatment failures in some studies.[13] This might be attributed to poor CNS penetration of crizotinib, with a concentration in cerebrospinal fluid almost 400-fold lower than that in the serum.[14] This lack of ALCL CNS disease control with crizotinib was also evidenced in a brief report by Ruf and colleague in 2018.[11] To overcome this problem, next-generation ALK inhibitors were designed to cross the blood-brain barrier more efficiently, thus achieving a higher concentration in the cerebrospinal fluid. As a result these molecules, which include ceritinib, alectinib, brigatinib and lorlatinib, demonstrated a prominent ability to control CNS disease in ALK-rearranged non-small cell lung cancer.[15]

We report here 11 neuro-meningeal relapses or progressions in ten patients with ALK-positive ALCL treated with next-generation ALK inhibitors. We first want to emphasize that this number is quite high as we report here ten patients with CNS relapses in 3 years compared to the previous 25 CNS relapses in nearly 20 years reported in the already mentioned European Inter-Group for Childhood Non-Hodgkin Lymphoma report.[3] This could be caused by some changes in our practices such as the wider use of vinblastine and the introduction of prolonged crizotinib treatment in a relapse setting, especially in patients with high-risk disease and in those who are positive

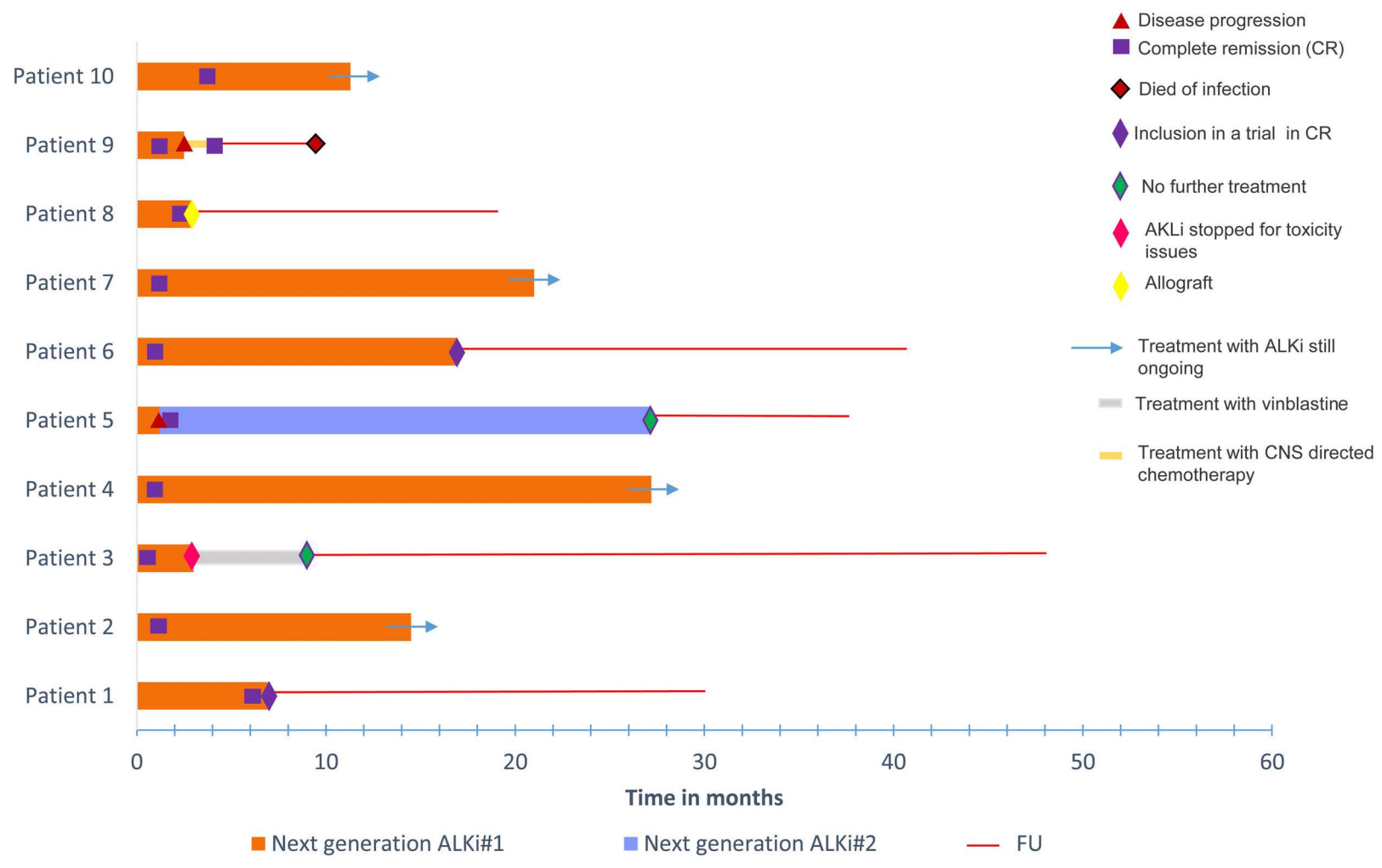

Figure 1. Swimmer-plot of French pediatric patients treated with next-generation ALK inhibitors for central nervous system relapse or progression of ALK-positive anaplastic large cell lymphoma. ALKi: ALK inhibitor; CNS: central nervous system; FU: follow-up.

for minimal residual disease. Of note, six of our patients relapsed on vinblastine or crizotinib. In this report of 11 CNS relapses treated with next-generation ALK inhibitors, a rapid, profound response was observed in all ten patients. Only one patient experienced secondary progression while on a next-generation ALK inhibitor whereas nine patients were still alive in complete remission at the last follow-up. Even though this series is small, the response rate and general outcome appears far better than that for relapsed/refractory ALK-positive ALCL with CNS involvement previously reported in the literature.[3]

The optimal duration of treatment with next-generation ALK inhibitors has not been assessed yet. Of note, although the majority of the patients achieved durable complete remissions, they may not be cured since abrupt relapses have been reported after the discontinuation of ALK inhibitors, even after several years of treatment.[16] In this series, one patient is still in complete remission after having stopped his treatment with an ALK inhibitor for nearly 1 year, with no further treatment.

In conclusion, despite the small number of cases, this report suggests a promising activity of next generation ALK inhibitors in patients with ALK-positive ALCL and CNS involvement at relapse. It also suggests that we should be more careful regarding the CNS prophylaxis of high-risk and relapsed ALK-positive ALCL and next-generation ALK inhibitors should be considered as part of CNS prophylaxis.

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Contributions

LB and CR planned the study. CR wrote the first draft of the manuscript. All the authors contributed to data control and to writing and revising the manuscript.

Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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